

Hypercholesterolemia and Dyslipidemia: Issues for the Clinician

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Opinion statement

The current state of the art in the diagnosis and treatment of lipoprotein disorders has progressed beyond the standard "lipid profile," which includes total low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol, along with fasting triglycerides. Incorporating aspects of the atherogenic lipoprotein profile (ALP) (ALP and LDL subclass distribution), HDL subclass distribution, apolipoprotein E isoforms, lipoprotein (a), homocysteine, and high-sensitivity C-reactive protein provides the clinician with the tools to create a more detailed, accurate, and personalized diagnosis of disorders contributing to coronary artery disease in their patients. Sophisticated laboratory tests are available to clinicians through technology transfer programs as exemplified by the Lawrence Berkeley National Laboratory/Berkeley HeartLab, Berkeley, CA, collaboration and allow clinicians access to research quality laboratory tools. This has significant clinical relevance because the presence of these disorders guides treatment that is specific to the disorder(s). Appropriate treatment has been shown to have significantly greater clinical benefit in patient subgroups exhibiting the disorder the therapy is most likely to correct. A single drug or lifestyle therapy plan is no longer appropriate for all patients. The treatment must match the individual disorder(s).

Introduction

Disorders of cholesterol and lipoprotein metabolism are at the heart of atherosclerosis and coronary artery disease (CAD) [1]. However, CAD is a metabolic disorder that is a complex interaction of genetic susceptibility and environmental factors that include diet, lifestyle habits, and factors that affect the inflammatory response [2,3]. Despite considerable success in the treatment of hypercholesterolemia, atherosclerosis remains the leading cause of death in most Western countries. Although cholesterol-lowering trials have revealed a 25% to 30% reduction in clinical events, a large number of patients continue to have events even when successfully treated with cholesterol-lowering medications (Fig. 1). Part of the reason for this less than optimal result is the fact that atherosclerosis is a multifactorial disease. Although disorders of lipoprotein metabolism

are found in a large number of patients with CAD, these disorders are very heterogeneous; single-drug therapy aimed at one disorder should not be expected to improve the disease status in the majority of patients [4]. Metabolic treatment still requires identification and treatment of patients with high cholesterol, but the focus has shifted to identifying high-risk patients in groups previously thought to be low risk, or identifying disorders coexistent with high cholesterol that are not corrected by standard cholesterol-lowering medications (Table 1) [5]. These disorders are common in patients with CAD even if they meet Adult Treatment Panel III low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) goals. The ability to detect high-risk CAD traits, which are often inherited, and predict response to treatment, has

substantially improved in the past few years. This allows identification of metabolic subgroups of patients that are different in regard to CAD risk prediction, and response to specific treatments. For example, in the Helsinki trial a 34% reduction in cardiovascular events was attributed to gemfibrozil in the entire population [6]. However, in the subgroup of patients with triglycerides greater than 204 mg/dL and LDL-C level and HDL-C level greater than 5.0 mg/dL, a 74% reduction in clinical events was reported [7]. Thus, most of the clinical benefit attributed to gemfibrozil treatment occurred in approximately 10% of the population that fit these lipid disorders. Sophisticated laboratory methods, which until recently were available only in research laboratories, provide physicians the opportunity to apply this knowledge to patient care and enter a new era of CAD risk factor detection and treatment. This allows a more scientific and individualized treatment approach than has previously been possible when the treatment approach was based on standard epidemiologic risk factors and a routine blood lipid profile [8].

The metabolism of lipoproteins follows a path of large particles, rich in triglycerides and relatively poor in cholesterol, which undergo a series of metabolic interactions that result in more dense particles that are relatively richer in cholesterol and poorer in triglycerides. Such triglyceride-rich particles derived from the liver, termed very low density lipoproteins, undergo interactions with lipase enzymes, which results in denser and relatively cholesterol-richer particles, termed intermediate-density lipoprotein (IDL), and eventually seven subclasses of low-density lipoprotein (LDL). It is important to appreciate these steps because medications designed to suppress only hepatic cholesterol synthesis do not impact other important steps in lipoprotein metabolism and leave disorders in this area uncorrected [9••].

High-density lipoprotein (HDL) is initially deployed in a discoid, relatively cholesterol-poor form, but following interaction with enzymes, cholesterol ester content is increased and the particle becomes less dense (more buoyant). Following interaction with transfer proteins and neutral exchange factors, cholesterol esters are transferred from HDL2 to a modified very low density lipoprotein, which eventually is identified as LDL-C [10]. The function of this pathway may be to play a role in what has been termed reverse cholesterol transport [11]. Disorders of reverse cholesterol transport can exist that are not reflected in HDL-C values. HDL2b, as assessed by gradient gel electrophoresis (GGE), is the HDL subclass most associated with CAD protection, and low values indicate increased CAD risk [12]. Individuals of Asian-Indian derivation have a threefold increased risk for CAD and appear to have a high incidence of reduced HDL2b

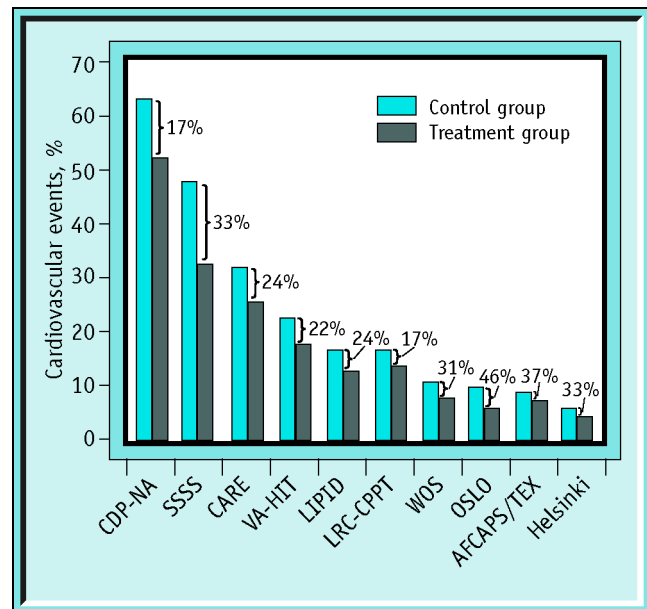


Figure 1. The results of large cholesterol-lowering clinical trials revealing the percent of subjects in the treatment and control groups that experienced a clinical event. Although a 25% to 30% reduction in events is laudable, a large number of patients taking the medications continue to have events. AFCAPS/TEX—Air Force Coronary Atherosclerosis Prevention Study/Texas; CARE—Cholesterol and Recurrent Events; CDP-NA—Coronary Disease Project—North America; LIPID—Long-term Intervention with Pravastatin in Ischemic Disease; LRC-CPPT—Lipid Research Clinics Coronary Primary Prevention Trial; SSSS—Scandinavian Simvastatin Survival Study; VA-HIT—High-density lipoprotein cholesterol Intervention Trial of the Department of Veterans Affairs; WOS—West of Scotland.

despite "normal" HDL-C levels [13]. An increase in the HDL2 region, attributed to nicotinic acid, has been shown to be a significant predictor of arteriographic benefit in patients with low HDL-C level [14••]. The large increase in HDL2b (127%) was masked by only a modest increase in HDL-C level (7%) in response to nicotinic acid therapy. Much greater change in HDL subclass distribution, compared with HDL-C, is often seen in response to therapies such as weight loss, diet, fibrates, and nicotinic acid.

Accurate determination of LDL and HDL subclasses is a moderately complex laboratory issue. The gold standard methods involve either analytic ultracentrifugation (ANUC) or polyacrylamide GGE [15]. These two methods have been used in a large number of both basic science investigations and clinical trials dating back to the groundbreaking work of Gofman *et al.* [16] in the 1950s and 1960s.

Many disorders of lipoprotein metabolism can now be diagnosed by the clinician and knowledge of these disorders allows treatment to be matched to the specific disorder(s) found in an individual patient. Many of these disorders are not directly linked to blood

Table 1. Metabolic disorders contributing to CAD*

| Disorder | Prevalence ATP-Yes | Prevalence ATP-No |
|---|-----------------------|----------------------|
| <i>N</i> | 203 (37%) | 346 (63%) |
| Small LDL (IIIa + IIb > 20%) | 49.3% | 73.6% |
| HDL2b < 20% | 53.3% | 88.3% |
| Lp(a) > 20 mg/dL | 31.8% | 32.1% |
| ApoE4 | 16.2% | 29.3% |
| Homocysteinemia (Hcy > 14 μ mol/L) | 8.1% | 39.4% |
| (Hcy > 10 μ mol/L) | 27.6% | 49.4% |
| hs-CRP > 0.40 mg/dL | 18.2% | 21.5% |
| Insulin > 12 uU/mL | 22.2% | 33.5% |

*A group of 549 patients with CAD who were seen by invasive cardiologists at the American Cardiovascular Research Institute in Atlanta, GA. The prevalence of the disorders is listed according to patients who met ATP-III LDL-C (< 100 mg/dL) and HDL-C (> 40 mg/dL) goals (ATP-Yes) and those who did not (ATP-No). In the entire group, 64.1% had LDL-C less than 100 mg/dL.

ApoE4—apolipoprotein E4; ATP—Adult Treatment Panel; CAD—coronary artery disease; Hcy—homocysteine; HDL-C—high-density lipoprotein cholesterol; HDL2b—high-density lipoprotein 2b; hs-CRP—high-sensitivity C-reactive protein; LDL—low-density lipoprotein; LDL-C—low-density lipoprotein cholesterol; Lp(a)—lipoprotein (a).

cholesterol, but elevations in LDL-C level compound the risk of these other disorders. Classic lipid disorders include elevated LDL-C level, elevated triglycerides, and low HDL-C level. Other, often more common disorders can now be diagnosed. The most common and clinically relevant disorders are reviewed in this article and they

include the following: atherogenic lipoprotein profile (ALP), elevated LDL-C level, apolipoprotein E (apoE) isoforms, elevated lipoprotein (a) [Lp(a)], familial combined hyperlipidemia (FCH), hypoalphalipoproteinemia, elevated plasma homocysteine, and elevated high-sensitivity C-reactive protein (hs-CRP) [17].

Treatment

Atherogenic lipoprotein profile

- Atherogenic lipoprotein profile is a collection of metabolic conditions that contribute to atherosclerosis risk. It is associated with insulin resistance, increased IDL, impaired reverse cholesterol transport, increased lipoprotein particle susceptibility to oxidation, and increased postprandial lipemia (Table 2) [18]. Although individuals exhibit seven LDL "types," ALP can be identified by the abundance of predominantly small, dense LDL particles (regions IIIa, IIIb, Iva, IVb on GGE, and Sf0-7 on ANUC), and it has also been termed LDL subclass pattern B, which can be compared with pattern A individuals who do not express this collection of conditions. ALP is a heritable trait that increases CAD risk three- to fivefold, independent of classic cardiovascular risk factors, and is associated with a twofold increased rate of arteriographic progression [19–21]. It identifies a group of patients with CAD who can have particularly good arteriographic outcomes with appropriate treatment [22,23].
- Fasting triglyceride values are often but not always elevated and HDL-C level is often but not always low in patients expressing LDL pattern B. Although fasting triglyceride values and other laboratory methods have a relationship to LDL peak particle diameter and statistically can divide large populations into probable pattern B and probable pattern A, within the fasting triglyceride range of 70 to 250 mg/dL, an error in individual subclass determination, using fasting triglyceride values, will be made in

Table 2. Metabolic derangements associated with the atherogenic lipoprotein profile

Abundance of small or dense LDL (regions IIIa, IIIb, IVa, IVb on GGE; Sf0-7 on ANUC)
 Abundance of IDL (Sf12-20 on ANUC)
 Low levels of antioxidants within lipoprotein particles
 Increased lipoprotein susceptibility to oxidation
 Insulin resistance
 Reduced HDL2 and HDL2b, implying impaired reverse cholesterol transport
 Increased postprandial lipemia
 Increased speed of LDL entry into the artery wall compared with large LDLs
 Increased proteoglycan binding
 Reduced uptake by the LDL receptor

ANUC—analytic ultracentrifugation; GGE—gradient gel electrophoresis; HDL2—high-density lipoprotein 2; HDL2b—high-density lipoprotein 2b; IDL—intermediate-density lipoprotein; LDL—low-density lipoprotein.

approximately 40% to 50% of cases [24,25•]. Thus, a fasting triglyceride value is not a clinically reliable tool for individual patient management within this range.

- Low-density lipoprotein subclass distribution is classically determined by ANUC, which provides a very accurate separation of particles based on density and Svedberg flotation intervals [26]. Although this method is detailed and precise, it is labor intensive and expensive. A second method that has been used in parallel with ANUC at the Lawrence Berkeley National Laboratory, Berkeley, CA, is GGE, which determines multiple LDL peak particle diameters (angstroms), position of peaks, and percent distribution in seven LDL regions [15]. By analyzing samples from clinical trials in parallel with these two techniques, GGE is an accurate and relatively inexpensive clinical tool to determine LDL subclass distribution, multiple LDL peaks, LDL subclass pattern, and response to treatment. Significant changes in LDL subclass distribution, seen as a reduction in small LDL balanced by an increase in large LDL, may occur despite no change in total LDL mass or LDL-C. This is exemplified by the results of the Stanford University Weight Loss Program, Stanford, CA (Fig. 2) [27].
- Atherogenic lipoprotein profile increases CAD risk threefold. It is present in 50% of male patients with CAD and in a large number of CAD patients with “normal” blood lipid values. ALP is associated with “impaired reverse cholesterol transport” as reflected by low HDL2b. It is an inherited trait (first-degree relatives are at risk); it identifies patients with CAD who are at risk for rapid arteriographic progression; and it identifies “good” arteriographic responders to treatment. ALP is associated with elevated triglyceride level and low HDL-C level but can be present even in the presence of normal triglyceride level and HDL-C level. It is also associated with type 2 diabetes mellitus and it increases lipoprotein particle susceptibility to oxidation.

Diet and lifestyle

- Low-fat, high-carbohydrate diets may exacerbate the trait and exercise and loss of excess body fat can improve the trait. Expression of the trait is an example of gene-environment interaction. Hypothyroidism can promote expression of the trait.

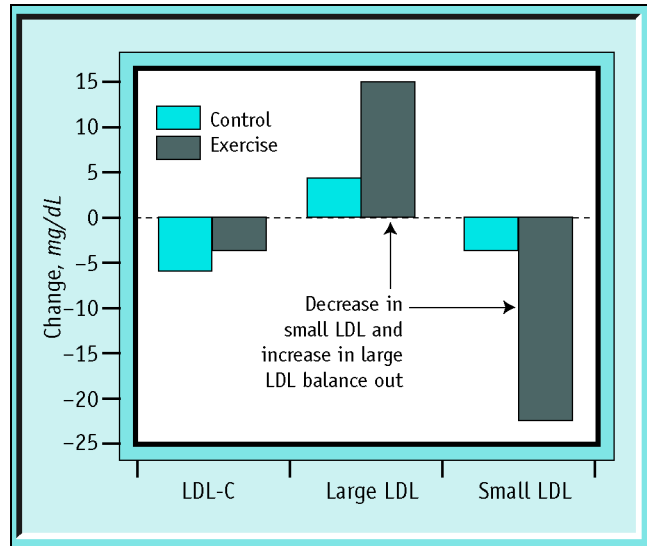


Figure 2. The significant change in small and large low-density lipoprotein (LDL) (determined by analytic ultracentrifugation), in response to exercise-induced weight loss, is masked by no change in routine measurement of LDL cholesterol (LDL-C) or LDL mass. The significant weight loss in the exercise group was not associated with a significant reduction in LDL-C. (From Williams *et al.* [27]; with permission.)

Pharmacologic treatment

- Nicotinic acid has been shown to improve LDL subclass distribution and increase HDL2b and it is a dose-dependent response. When triglyceride levels are reduced to 140 to 160 mg/dL, substantial shifts in LDL subclass distribution away from the small to the large regions can be seen. Fenofibrate and gemfibrozil can have a beneficial effect on LDL subclass distribution.
- The combination of nicotinic acid and a fibrate drug can be particularly useful in combined hyperlipidemia and the dyslipidemia, which are often seen in type 2 diabetes. The combination allows lower doses of nicotinic acid to be used. The combination of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor drug and nicotinic acid can substantially reduce LDL-C level and improve the LDL subclass distribution. Hormone replacement therapy (HRT) may improve the LDL and HDL subclass distribution, β -blocker medications may exacerbate the small LDL trait, and α -blockers may improve the small LDL trait.

Nicotinic acid

Nicotinic acid has been used for many years to treat dyslipidemias and is particularly effective in treating the small LDL trait. It has been used in multiple clinical trials and is associated with improved clinical outcomes.

Standard dosage 1000 to 5000 mg/d are common doses. The lipid response is dose dependent. Immediate-release niacin is dosed three times a day and a slow titration is important to successful implementation. 100 mg three times a day, increasing by an additional 100 mg three times a day every 3 to 5 days is an acceptable titration schedule. The effect on plasma lipids is generally assessed when the patient is in the 1000 to 1500 mg/d range. Once-a-day niacin is available and has the advantage of once-daily dosing, which has been shown to improve compliance. The US Food and Drug Administration recently approved a once-a-day niacin with toleration superior to immediate-release niacin and another combination pill of nicotinic acid and lovastatin.

| | |
|--------------------------------|---|
| Contraindications | Nicotinic acid may exacerbate peptic ulcer disease or gastrointestinal (GI) distress; it may exacerbate ulcerative colitis; it may increase the potential for atrial fibrillation; and it may increase uric acid. It should not be used in individuals with liver dysfunction. |
| Main drug interactions | Nicotinic acid may exacerbate hepatotoxic effects of other medications. |
| Side effects | Nicotinic acid may cause a prostaglandin-mediated vasodilation associated with redness, itching, and flushing. By increasing uric acid it may exacerbate gout. High doses have been associated with myositis and atrial fibrillation in men with existing CAD. It may be associated with the development of acanthosis nigricans and it may increase blood glucose, but it can be used in diabetic patients with due caution to diabetic control. |
| Cost/cost-effectiveness | Nicotinic acid is the most cost-effective lipid-lowering agent. |

Fibric acid derivatives

| | |
|--------------------------------|---|
| | The fibric acid derivatives, clofibrate, gemfibrozil, and fenofibrate, have been used to treat hyperlipidemias for several decades. They are quite effective in reducing elevated triglyceride levels and triglyceride-rich lipoproteins. They have been reported to reduce uric acid levels. |
| Standard dosage | Clofibrate: 500 mg twice a day. Gemfibrozil: 600 mg twice a day. Fenofibrate: 200 mg/d. |
| Contraindications | These agents should not be used in individuals with liver dysfunction. Use in patients with renal dysfunction is a relative contraindication based on the etiology of the renal dysfunction; pregnancy and lactation are other contraindications. |
| Side effects | These agents are generally well tolerated. They may be associated with some GI distress, and in combination with HMG-CoA reductase inhibitors, may result in elevated creatine kinase and potentially rhabdomyolysis, although this later effect appears to be rare. |
| Cost/cost-effectiveness | These agents have moderate cost-effectiveness and some are available in generic form. |

Hypercholesterolemia

- Hypercholesterolemia is generally defined as an LDL-C level greater than 160 mg/dL. The National Cholesterol Education Program has presented guidelines that suggest an LDL-C goal of less than 130 mg/dL is appropriate for individuals without known CAD, and less than 100 mg/dL for individuals with CAD [28]. The classic high LDL-C disorder is familial heterozygous hypercholesterolemia (FH). Initially recognized in the 1930s, FH is a well-characterized disorder that includes over 30 inherited defects, which result in a dysfunctional LDL receptor [29]. It affects approximately one in 500 of the general population and approximately 3% of patients with CAD. The resultant elevation in plasma LDL-C level to values, generally in excess of 250 mg/dL, is associated with an average age of onset of CAD of approximately 45 years in men and 55 years in women [30]. Familial defective apo B is an inherited disorder that exhibits LDL-C values in the same range as FH and is due to a defective apo B protein, which has been identified as a single nucleotide mutation at codon 3500 that results in an arginine substitution [34]. It occurs in approximately one in 500 people in the general population and is associated with an LDL-C level between 270 to 370 mg/dL [31].
- Multiple clinical trials have convincingly demonstrated that reduction of elevated LDL-C level results in a reduction in cardiovascular events and can slow the rate of arteriographic CAD progression in some, but not all patients. This is particularly important for patients with elevated LDL-C

level. The benefit can be seen both in patients without established CAD (primary prevention) and in those with established CAD (secondary prevention) [4].

- Hypercholesterolemia contributes to atherosclerosis, is easy to detect, and it may be inherited. It is exacerbated by an “unhealthy” lifestyle, which includes sedentary nature and high-fat diets. Treatment reduces cardiovascular events and arteriographic rates of progression.

Diet and lifestyle

- A reduced-fat diet is the foundation of an LDL-C-lowering therapy. American Heart Association phase I or II diets are useful. Loss of excess body fat or exercise does not reduce LDL-C level unless diet composition is also altered. Decaffeinated or boiled coffee may increase total cholesterol by approximately 4% to 8% and dietary fiber or supplemental fiber may reduce total cholesterol by approximately 4% to 8%.

Pharmacologic treatment

- The bile-acid-binding resins have been used for two decades to reduce elevated LDL-C level. HMG-CoA reductase inhibitors significantly improved the ability of physicians to reduce elevated LDL-C level. Nicotinic acid and fenofibrate can reduce LDL-C level moderately but not as much as the HMG-CoA reductase inhibitors. The combination of resin plus statin or resin plus statin plus niacin or fenofibrate can be particularly effective in reducing elevated LDL-C level.

Bile-acid-binding resins

| | |
|--------------------------------|--|
| Standard dosage | Colestipol: 5 to 30 g/d in packets mixed with liquid, or 1 to 10 g/d tablets. Cholestyramine: 9 g/d packets contain 4 g of anhydrous cholestyramine resin. Daily dose is 8 to 24 g of anhydrous cholestyramine. Colesevelam hydrochloride: 625-mg tablets, 1 to 3 tablets twice a day. |
| Contraindications | Constipation and GI disease are relative contraindications. The physician must use clinical judgement. |
| Main drug interactions | Resins may bind other medications and reduce or prevent adsorption. These drugs include, but are not limited to, warfarin, thyroid medications, gemfibrozil, tetracycline, fat-soluble vitamins, digoxin, and hydrochlorothiazide. |
| Side effects | Side effects are mainly GI. Hardening of the stool and constipation may occur and is dose related but may be improved with standard constipation treatment. Excess bowel gas may be experienced. |
| Cost/cost-effectiveness | These drugs have moderate cost-effectiveness. |

HMG-CoA reductase inhibitors

| | |
|--------------------------|--|
| Standard dosage | Atorvastatin: 10 to 80 mg/d. Fluvastatin: 20 to 80 mg/d. Lovastatin: 10 to 80 mg/d. Pravastatin: 10 to 40 mg/d. Simvastatin: 5 to 80 mg/d. |
| Contraindications | The HMG-CoA reductase inhibitors may contribute to liver dysfunction. They may also cause elevations in transaminase levels. Use with antibiotics of the erythromycin class may increase the risk of liver dysfunction or myositis. They should be used with caution in those at risk of myositis, and there is potential interaction with renal dysfunction and other agents such as fibrates, niacin, and immunosuppressive drugs. Pregnancy and lactation are other contraindications. The combination of simvastatin |

and nicotinic acid may increase the risk of myositis. Cerivastatin is no longer available due to a relatively high incidence of fatal rhabdomyolysis compared with other compounds in this class (Table 3) [32].

Main drug interactions These drugs may slightly potentiate the effect of warfarin. The combination of a statin with niacin or fibrate may exacerbate the risk of liver dysfunction or myositis, but combination therapy can be quite effective in correcting lipoprotein disorders [33]. Simvastatin is a substrate for CYP3A4, and inhibitors of CYP3A4 may increase the risk of myopathy by increasing the concentration of HMG-CoA reductase inhibitory activity and include cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice (> 1 qt/d) [34].

Side effects These drugs are generally well tolerated, but GI distress, myalgia, and rash have been reported in a small number of patients. Interaction of statin plus gemfibrozil and the CYP3A4-mediated oxidation of a statin appears to be different for simvastatin and cerivastatin in dogs [35•]. This may help explain the different side effects of various statin drugs.

Cost/cost-effectiveness These drugs have moderate cost-effectiveness.

Apolipoprotein E isoforms

- One of the most common genes affecting LDL-C levels codes for apoE, which has three major isoforms designated as E2, E3, and E4 [36]. ApoE with a normal amino acid sequence is termed E3. Abnormal amino acid substitutions can result in E proteins termed E2 or E4. The most common allele, E3, has a frequency of approximately 0.78, whereas E4 has a frequency of 0.15, and E2 a frequency of 0.07. In addition, analysis of amino acid substitution has revealed at least 25 mutations in apoE.
- The fractional catabolic rate of LDL is reduced in individuals with the apoE4 genotype; this may be related to enhanced clearance of apoE4-containing remnants and suppression of LDL receptors [37]. ApoE4 is a common contributor to elevated LDL-C level and is found in approximately 25% of the population. Postprandial lipid metabolism differences exist between apoE 3/4 subjects and normal apoE 3/3 subjects [38,39]. The disease, type III hyperlipoproteinemia, is an example of an interaction of the apoE2 homozygous state with another genetic or environmental factor, leading to marked accumulation of triglyceride-rich lipoprotein remnants and accelerated atherosclerosis [40].
- Apolipoprotein E isoforms are commonly inherited contributors to lipoprotein disorders. They are relatively easy to detect and may be linked to Alzheimer's disease risk [41]. The plasma lipoprotein profile can be exacerbated by "unhealthy" lifestyle and diets. The apoE 2/2 isoform creates the potential for type III hyperlipidemia.

Diet and lifestyle

- Reduced-fat diet is the foundation of an LDL-C-lowering therapy. Patients with the apoE4 allele have significantly greater LDL-C reduction in response to a low-fat diet than apoE 3/3 individuals [42]. Type III hyperlipidemia is very sensitive to environmental issues such as body fat and diets rich in simple carbohydrates.

Table 3. Incidence of fatal rhabdomyolysis*

| | Lovastatin | Pravastatin | Simvastatin | Fluvastatin | Atorvastatin | Cerivastatin | Total |
|--|------------|-------------|-------------|-------------|--------------|--------------|-------|
| Approval, y | 1987 | 1991 | 1991 | 1993 | 1996 | 1997 | |
| Fatal rhabdomyolysis cases, <i>n</i> | 19 | 3 | 14 | 0 | 6 | 31 | 73 |
| Prescriptions × 10 ³ , <i>n</i> | 99,197 | 81,364 | 116,145 | 37,392 | 140,360 | 9,815 | — |
| Reporting rate (per one million prescriptions) | 0.19 | 0.04 | 0.12 | 0 | 0.04 | 3.16 | 0.15 |

*Based on when the HMG-CoA reductase inhibitor was approved, the number of fatal cases, the number of prescriptions written, and the calculated reporting rate.

HMG-CoA—3-hydroxy-3-methylglutaryl coenzyme A.
(Modified from Staffa et al. [32].)

Pharmacologic treatment

- An LDL-C reduction in patients with the E4 allele can be achieved with resins, statins, and niacin. The dyslipidemia of type III hyperlipidemia can be treated with fibrate drugs and niacin [43].

Lipoprotein (a)

- Lipoprotein (a) (Lp[a]) is an LDL particle with the protein apo (a) attached by a disulfide bridge. The protein (a) has structural similarities to plasminogen and consists of multiple repeats of amino acid sequences termed “kringles” (due to their similar appearance to a Dutch pastry called a “kringle”). This inherited disorder appears to increase CAD risk and is particularly powerful in the presence of other risk factors. Lp(a) may contribute to atherosclerosis by a variety of mechanisms, including interference with thrombolysis, binding to fibrinogen, and susceptibility to oxidative damage [44]. Mean Lp(a) values determined in the Atherosclerosis Risk in Communities Study have been reported to be approximately 4 mg/dL for middle-aged men and women and 18 to 21 mg/dL for the 90th percentile of a healthy population [45].
- The evidence that Lp(a) is a CAD risk factor is derived from numerous epidemiologic and clinical trials. Rapid progression of arteriographically determined CAD has been shown to be significantly more common in subjects with Lp(a) greater than 25 mg/dL [46]. Lp(a) has been noted to be an independent risk factor for myocardial infarction in young men, is independently associated with arteriographically defined coronary disease, and has been reported to be present in high levels, in approximately 50% of children of patients with high Lp(a) [47–50]. The CAD risk prediction power of Lp(a) is increased in individuals who also exhibit elevated LDL-C [51].
- One clinical investigation has demonstrated a link between Lp(a) reduction with plasmapheresis and a significant reduction in restenosis following angioplasty. Another investigation demonstrated a reduction in arteriographic progression when LDL-C was substantially reduced in the presence of elevated Lp(a) [52,53]. Specific benefit in regard to a significant reduction in cardiovascular clinical events was reported when Lp(a) was reduced with HRT in HERS (Heart and Estrogen-progestin Replacement Study) [54••].
- Elevated levels of Lp(a) are found in approximately 33% of patients with CAD. Laboratory test reliability is a problem. Lp(a) is inherited in a dominant fashion, so the physician should consider screening family members. Lp(a) exacerbates the CAD risk associated with other risk factors.

Diet and lifestyle

- Lifestyle intervention does not appear to impact Lp(a) values and Lp(a) has a small response as an acute-phase reactant.

Pharmacologic treatment

- Lp(a) reduction has been reported with nicotinic acid [55–58], HRT, estrogen, tamoxifen, testosterone, and neomycin. Lp(a) reduction has not been reliably associated with HMG-CoA reductase inhibitors or fibrate medications [59].

Familial combined hyperlipidemia

- Elevations in both triglyceride and LDL-C levels in families with a history of CAD or hyperlipidemia have been termed familial combined hyperlipidemia (FCH); they are accompanied by a three- to fourfold increased risk for CAD [60]. In this condition, plasma lipids can be variably expressed as elevated LDL-C level alone, elevated triglyceride levels alone, or a combination at various times. One first-degree relative must exhibit one of the lipid abnormalities or CAD to complete the diagnosis of FCH. The variability in phenotypic expression has involved a number of related disorders, including LDL subclass pattern B, hyperapobetalipoproteinemia [61], familial dyslipidemic hypertension [62], and syndrome X [63]. The genetics of this disorder are unclear, in part due to the combination of probably multiple genetic causes interacting with multiple environmental conditions to create similar phenotypes [64].
- Familial combined hyperlipidemia is present in approximately 20% of patients with CAD. Triglyceride and LDL-C values can vary from test to test. FCH is inherited in a complex fashion, so physicians should consider screening family members. It is associated with the ALP, it increases CAD risk fourfold, and it increases lipoprotein particle oxidation susceptibility.

Diet and lifestyle

- Exercise and reduced-fat diet can improve the condition. Diets rich in simple carbohydrates and excess body fat can worsen the condition [65].

Pharmacologic treatment

- Combined drug therapy is often necessary to treat the combination of elevated LDL-C and triglyceride levels successfully [66]. Resin plus niacin or a fibrate can be effective; resins may exacerbate the elevated triglycerides; statin plus niacin or a fibrate can be effective; and resin combined with statin and niacin or a fibrate can be effective.

Hypoalphalipoproteinemia

- Low HDL-C level has been determined to be a CAD risk factor in numerous epidemiologic and clinical trials, but its exact role is often unclear owing to the often-associated high triglyceride level or abundant small LDL or IDL, which are known to be atherogenic. Mortality in patients with CAD has been linked to HDL-C values. In the Coronary Drug Project, 5-year mortality was 33% for men with an HDL-C less than 35 mg/dL ($P = 0.03$)

[67]. The Israeli Ischemic Heart Disease Study found the highest 15-year mortality rate (74%) was in patients who had experienced a myocardial infarction and who had an HDL-C level less than 30 mg/dL [68]. HDL subfractions have also been shown to help predict CAD severity and arteriographic progression; lower HDL2b portends greater risk [69]. Treatment that increases HDL-C level, and in particular HDL2 (Lp[A1]), has been shown to be associated with significant arteriographic benefit and a dramatic reduction in cardiovascular events [14••].

- The term hypoalphalipoproteinemia is generally reserved for very low HDL. The condition is thought to have a genetic etiology, transmitted in an autosomal-dominant fashion, and strongly linked to premature CAD [70]. Hypoalphalipoproteinemia can be defined as an HDL-C value lower than the 10th percentile, which is less than approximately 29 mg/dL for middle-aged men and less than 38 mg/dL for middle-aged women. As many as 36% of men with premature CAD have been reported to express a version of this trait, which is a broad spectrum of overlapping disorders [71]. One genetic cause is a polymorphism in the region between the apolipoprotein A-I and apolipoprotein C-III, which results in low HDL values and in these cases elevated triglyceride levels are not common, and isolated low HDL is the main contributor to premature CAD [72].
- Low HDL-C is found in 20% to 30% of patients with CAD. There is a complex interaction of lifestyle and impact of triglyceride level. Primary hypoalphalipoproteinemia is found in approximately 5% of patients with CAD. HDL2b can be low in the setting of "normal" HDL-C values; this reflects impaired reverse cholesterol transport. Low HDL2b is associated with coronary artery arteriographic severity and disease progression. An increase in HDL2 and Lp(A1) is associated with arteriographic benefit.

Diet and lifestyle

- Loss of excess body fat and increased physical activity may increase HDL-C level. Alcohol may increase HDL-C level, but it appears to be HDL3. (Alcohol consumption is not recommended as a method of increasing HDL-C level.) Cigarette smoking may reduce HDL-C level.

Pharmacologic treatment

- In the setting of true hypoalphalipoproteinemia, treatment is often unsuccessful [73,74]. In the setting of elevated triglyceride level, reduction of triglyceride level with niacin or fibrates may increase HDL-C level. Niacin may increase HDL-C level even in the setting of "normal" triglyceride levels. If an increase in HDL-C level is not achieved, consider reduction of LDL-C level to improve the LDL-C:HDL-C ratio. Niacin increases HDL2 mass more than HDL3 mass. Resins and statins have little effect on hypoalphalipoproteinemia.

Homocysteine

- Substantial evidence exists that links elevated homocysteine levels to peripheral and coronary atherosclerosis [75,76]. Most recently, the European Concerted Action Projects confirmed that elevated homocysteine levels were an independent risk factor for atherosclerosis [77]. There was a 2.2 increase in relative risk for fasting values in excess of 12 $\mu\text{mol/L}$. Following percutaneous coronary intervention (PCI), restenosis rates (25% vs 50%, $P < 0.001$) and major adverse cardiac events (16% vs 28%, $P < 0.05$) were significantly less in patients with homocysteine levels lower

than 9 $\mu\text{mol/L}$ [78•]. In patients with established CAD, homocysteine levels greater than 10 $\mu\text{mol/L}$ have been associated with a significant increase in mortality [79]. Most recently, treatment of post PCI patients with B vitamins (folate 1 mg/d), cyanocobalamin (400 $\mu\text{g/d}$), and pyridoxine (10 mg/d) has resulted in a significant reduction in restenosis rates [80••]. Some lipid-lowering therapies may increase plasma homocysteine levels.

- Homocysteine increases CAD risk two- to threefold and it increases the risk of restenosis following PCI. Elevated levels of homocysteine are associated with impaired vasoreactivity and in CAD patients, with increased mortality. Homocysteine levels may reflect other metabolic issues such as pernicious anemia or renal disease. Treatment can reduce restenosis rates.

Diet and lifestyle

- Foods high in methionine content (precursor of homocysteine) include meat, poultry, fish, and dairy products. Foods low in methionine or rich in B vitamins include, soy protein, complex carbohydrates, fruits, and vegetables.

Pharmacologic treatment

- A standard dose of folic acid is 1 to 5 mg/d. A standard dose of pyridoxine (vitamin B₆) is 25 to 200 mg/d. A note of caution: high-dose B₆ may result in a permanent peripheral neuropathy. Nicotinic acid [81] and fenofibrate [82•] may increase plasma homocysteine levels [81]. Antiepileptic drugs may be associated with increased plasma homocysteine levels [83].

High-sensitivity C-reactive protein

- C-reactive protein (CRP) is an acute-phase protein reactant that can achieve very high levels in a relatively short period of time following an inflammatory insult [84]. Assessment of high-sensitivity CRP (hs-CRP), in the primary prevention population, may be most valuable in the presence of other, more traditional, risk factors. In the Women's Health Study, women in the highest hs-CRP quartile had a relative risk of 4.4 ($P = 0.001$), whereas women in the highest total cholesterol quartile had a relative risk of 2.4 ($P < 0.003$). However, women with the combination of both elevated hs-CRP and elevated total cholesterol revealed a relative risk significantly higher than either hs-CRP or total cholesterol alone [85•]. A similar relationship of hs-CRP and traditional blood lipid measurements was reported in men from the Physicians' Health Study [86]. Multivariate analysis models, incorporating CRP and lipid measurements, resulted in significantly better risk prediction ($P < 0.003$) than either alone. The highest relative risk of 5.3 was found in the men with both elevated total cholesterol greater than 223 mg/dL and elevated hs-CRP greater than 1.69 mg/L. In patients with unstable angina, CRP values greater than 1.5 mg/L may be a strong independent marker of increased 90-day event risk, and values greater than 10 mg/L, of death [87,88]. Likewise, in patients who had a coronary artery bypass graft, values greater than 3 mg/L appear to have an increased risk of ischemia 1 to 6 years after surgery [89].

- Elevated hs-CRP levels identify patients at increased risk for cardiovascular events. The combination of elevated hs-CRP and another risk factor, such as elevated LDL-C level, compounds the risk attributed to hs-CRP alone. Elevated hs-CRP levels in the CAD and post-CABG populations identify patients at increased risk for cardiovascular complications. The hs-CRP level may be elevated owing to factors not linked to CAD.

Pharmacologic treatment

- Aspirin reduces cardiovascular risk the most in patients with elevated hs-CRP level [90]. Patients with elevated hs-CRP level treated with a statin appear to have the most benefit in regard to cardiovascular event reduction compared to those without elevated hs-CRP. Reductions in hs-CRP levels have been reported following treatment with statins, nicotinic acid, and fenofibrate. The following medications have been shown to have no effect, or an unclear effect, on hs-CRP levels: aspirin, ciglitazone, HRT, and ticlopidine.

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