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Hyperlipidemia and Management

Hyperlipidemia (HLP) is a common condition that crosses multiple medical practices. Beyond the isolated diagnosis, it is associated with metabolic syndrome, diabetes, and obesity as well as causative in coronary artery disease, peripheral arterial disease, and stroke. Similarly to hypertension (HTN), it can be a "silent killer" with no known signs or symptoms until an index event. Primary care physicians should test for HLP with routine blood work as part of cardiovascular risk evaluation. Once HLP is detected, treatment should begin. The cornerstone of treatment is lifestyle modification.

Due to the difficulty in patients making significant lifestyle change, pharmacotherapy is often needed. Current data show that less than 5% of myocardial infarction (MI) and stroke survivors make comprehensive lifestyle changes. There has been a rapid evolution in the amount of evidence-based data in this area and it is now clear that statins offer the only real proven mortality and cardiovascular event reduction benefit in patients with HLP. Bile acid sequestrants have a modest impact on lipids with a similar modest effect on cardiovascular outcomes, but not mortality. There may still be a role for ezetimibe, fibrates, and niacin for the truly statin-intolerant patients.

Although statins have a wide and safe therapeutic window, they are not without side effects, thus further emphasizing the importance of lifestyle modification. This is even more important — as the recently released guidelines and the new Pooled Cohort Equations Risk Calculator call for an almost doubling of patients on statins. These same guidelines and new risk calculator have led to substantial controversy, which will be discussed in detail.

Now, more than ever, it is important to assess patients' cardiovascular risk, discuss options with the patients (starting with lifestyle modification), and be aware of the best evidence-based approaches to drug therapy.

Definition of the Problem

HLP is an excess of lipids and lipoproteins in blood. These lipids include triglycerides, cholesterol, cholesterols esters, and phospholipids. The term hyperlipidemia has been used synonymously with hypercholesterolemia, hypertriglyceridemia, and hyperlipoproteinemia. HLP can be due to genetic polymorphisms or secondary to metabolic syndrome, diet, physical inactivity, and medications.[1]

HLP is important to the pathogenesis of cardiovascular disease (CVD) because it is a modifiable risk factor for atherosclerotic disease and a predictor of ischemic events.[2] Atherosclerosis is a dynamic process leading to progressive narrowing of arteries. This process is mediated by infiltration of the intima by inflammatory cells (T cells and monocytes), smooth muscle cells, and lipids.[2]

Epidemiology and Pathophysiology

CVD is major cause of morbidity and mortality worldwide. The Framingham Heart Study showed the lifetime risk of CVD in patients age > 40 years to be 49% in males and 32% in females. Even though there has been a decline in the

Executive Summary

The recently published ACC/AHA guidelines for the management of hyperlipidemia have elicited considerable controversy, particularly for the movement away from targeting LDL levels and for the perceived raising of the indications for statin therapy.

- Cardiovascular disease remains a major cause of mortality and morbidity.
- Hyperlipidemia affects approximately 71 million Americans and less than half are receiving treatment.
- Per ATP-III, lipoprotein measurements should be done once every 5 years in otherwise low-risk persons.
- Treatment of hyperlipidemia includes lifestyle modification and pharmacologic intervention, most commonly with statins.
- The new guidelines no longer focus on treatment to targeted LDL levels but rather focus on assigning patients to moderate or high-intensity statin treatment.
- Pooled cohort equation risk calculators have supplanted the Framingham Risk Score and are readily accessible through a cell phone application that can be used to better predict coronary heart disease risk over 10 years and help to determine which patients would better benefit from lifestyle and pharmacologic treatment.

overall mortality from CVD in the last decade, CVD remains the major cause of mortality in developed countries, claiming more than 1 million American lives annually. The prevalence of CVD is on the rise. The modifiable risk factors leading to CVD as outlined in the worldwide INTERHEART study include HTN, HLP, diabetes, abdominal obesity, smoking, alcohol intake, depression, lack of exercise, and lack of intake of fruits and vegetables.[3] Evaluation of these modifiable risks is of paramount importance in managing patients with CVD.

According to the Centers for Disease Control and Prevention (CDC) 2012 data, approximately 71 million American adults (33.5%) have HLP and less than 50% of them are receiving treatment. People with high total cholesterol have approximately twice the risk of heart disease as people with optimal levels. There is direct correlation between the level of cholesterol and risk of CVD. An increase of 1 mg/dL in serum low-density lipoprotein cholesterol (LDL-C) or a decrease of 1 mg/dL in high-density lipoprotein cholesterol (HDL-C) is associated with 2-3% increased risk or 3-4% increased risk of CVD, respectively. Furthermore, a 1-unit decrease in total cholesterol or LDL-cholesterol to HDL-cholesterol ratio is associated with 50% reduced risk of MI.

There has been a steady downward trend in serum cholesterol levels over the years.[4] The percentage of adults with a total cholesterol level of at least 240 mg/dL (≥ 6.22 mmol/L) decreased from 20% during 1988-1994 to 17% during 1999-2002 ($P < 0.001$).[4] Although there has been improved survival in patients with CVD with modification of population risk factors, such as HLP, smoking, HTN, and physical activity, the improvement in mortality and life-years gained was partially offset by substantial increases in obesity and diabetes. There were 308,900 fewer CVD deaths in 2000 among Americans aged 25-84 years than if 1980 mortality rates had applied. These fewer deaths represented approximately 3,147,800 life-years gained, which were diminished by a loss of 715,000 life-years attributable to increased rates of obesity and diabetes.[5]

The World Health Organization (WHO) definition of overweight is a body mass index (BMI) ≥ 25 kg/m^2, and obesity is defined as a BMI ≥ 30 kg/m^2. Currently, 67% of the U.S. population is either overweight or obese.[6] According to 2012 CDC data, childhood obesity has more than doubled in children and quadrupled in adolescents in the past 30 years. In the United States, children aged 6-11 years and adolescents aged 12-19 years who are obese increased from 7% to 18% and 5% to 21%, respectively, between 1980 and 2012.[7] Obese youth are at high risk of developing cardiovascular risk factors such as HLP, HTN, and prediabetes. They are more likely to be obese as adults and at risk of CVD, type 2 diabetes, stroke, sleep apnea, certain types of cancers, and osteoarthritis. The annual medical cost of obesity in the United States was $147 billion in 2008.

It is on this background that metabolic syndrome has emerged as a worldwide epidemic and public health care problem. Metabolic syndrome is defined by any three or more of the following criteria: central obesity (waist circumference ≥ 102 cm in men and ≥ 88 cm in women), HTN (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or drug treatment for HTN), decreased HDL (< 40 mg/dL in men and < 50 mg/dL in women, or drug therapy for reduced HDL), and elevated triglycerides (≥ 150 mg/dL, or drug treatment for elevated triglycerides) with insulin resistance (fasting plasma glucose ≥ 100 mg/dL, or therapy for hyperglycemia) as the uniting physiologic factor.[8] The prevalence of metabolic syndrome among adults ≥ 20 years of age was found to be 34% in a National Health and Nutrition Examination Survey (NHANES) during 2003-2006 in the United States.[9] The prevalence of metabolic syndrome increased with age and varied by race, ethnicity, and sex. Females > 60 years of age were more likely than men to meet the criteria for metabolic syndrome compared to the youngest age group. Nonalcoholic fatty liver disease is now

recognized to be the hepatic component of metabolic syndrome, which along with its individual components — particularly diabetes and elevated triglycerides — is the major risk factor for the development of nonalcoholic steatohepatitis (NASH), the most severe form of nonalcoholic fatty liver disease.[10] NASH may progress to liver cirrhosis, hepatocellular carcinoma, and liver failure.[10] Currently, NASH is the third most common cause of liver transplantation, but it is projected to be the leading cause in 2020.

The ultimate result of metabolic syndrome is development of diabetes and CVD. Diabetes is now considered a coronary heart disease equivalent. HLP plays a primary role in this process, with initiation and progression of atherosclerosis. Low HDL-C and high LDL-C are risk factors for CVD. Oxidatively modified LDL particles are taken up by macrophages in the subendothelial space with subsequent generation of cholesterol-rich foam cells. The acute rupture of atherosclerotic plaques leads to coronary luminal obstruction and acute coronary syndromes. Matrix-metalloproteinases (MMP) cause interstitial collagen degradation, promoting plaque instability and rupture. Besides decreasing cholesterol, statins have other pleiotropic effects. These include reduced inflammation, increased levels of interstitial collagen, reduced expression of interstitial collagenase (MMP-1), lower levels of oxidized LDL, reduced production of reactive oxygen species, increased expression of endothelial nitric oxide synthase, reduced thrombotic potential, and increased fibrinolytic potential.[11]

There are medical and surgical treatment options for obesity. The medical therapy approach involves behavioral therapy, increased physical activity, reducing caloric intake, and various pharmacotherapies. Bariatric surgery reverses some of the changes seen in metabolic syndrome compared to non-surgical treatments. In a recent meta-analysis of 11 studies, Gloy et al concluded that patients with morbid obesity, BMI 30-52 kg/m^2, and bariatric surgery had higher remission rates of type 2 diabetes and metabolic syndrome, higher HDL-C, and decreased triglycerides compared to non-surgical treatment.[12] Though the results of this meta-analysis are limited to 2 years of follow-up and a small number of studies and patients, they do point to the potential benefit of surgery for this serious public health problem. The current guidelines recommend BMI > 40 kg/m^2 or > 35 kg/m^2 with serious comorbidities as criteria for evaluation for bariatric surgery.

Clinical Features

Clinical features of HLP include peripheral arterial disease, stroke, CVD, pancreatitis due to elevated triglyceride and xanthomas, and skin lesions high in lipid content that can be seen in patients with familial hypercholesterolemia. It is also important to remember that HLP could also be a secondary cause of another underlying disease such as obesity, liver disease, hypothyroidism, Cushing's syndrome, and certain drugs like thiazides and cyclosporine.[13] As such, patients with other disease processes may have clinical features that might alert to the possibility of HLP.

Diagnostic Studies

Clinical diagnosis of HLP is made primarily by a fasting lipid profile, which requires fasting for about 12 hours prior to the test. Published reports have suggested that non-fasting lipid profile is just as effective as fasting lipid profile.[14] The lipid profile measures total cholesterol, HDL, and triglycerides; from the formula total cholesterol-HDL-triglyceride/5, a calculated LDL can be obtained. LDL can be measured directly but the value is sometimes underestimated.[15] If the lipid profile is taken in a non-fasting state, only the values of total cholesterol and HDL are useful.[16]

As per Adult Treatment Panel III (ATP III), lipoprotein measurements once every 5 years are adequate in otherwise low-risk persons. For those with multiple risk factors or in those with 0-1 risk factors with LDL-C above risk-stratified goal, more frequent measurement will be required. A non-fasting lipid profile can be used in low-risk persons (0-1 risk factor) and if the HDL-C level is ≥ 40 mg/dL and total cholesterol is < 200 mg/dL, no further testing is required. However, for individuals with multiple CVD risk factors (> 2), lipoprotein measurement is recommended as a guide to clinical management and, hence, a fasting lipid profile should be obtained.[16] Lipid profile ranges are included in Table 1.

Table 1: ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol: Primary Target of Therapy	
< 100	Optimal
100-129	Near optimal
130-159	Borderline high
160-189	High
≥ 190	Very high
Total Cholesterol	
< 200	Desirable
200-239	Borderline high
≥ 240	High
HDL Cholesterol	
< 40	Low
≥ 60	High

Table 2: An Apple a Day Keeps the Doctor Away

	Apple a Day	Generic Statin
Annual death reduction	8500 deaths	9400 deaths
95% confidence interval	6200-10,800	7000-12,500
Side effects	None	1200 more cases of myopathy 200 more cases of rhabomyolysis 12,300 new cases of diabetes

Table 3: The 5 A's

Call to Action for Better Population Health Through Behavior Change
1. Assess the behavior
2. Advise change
3. Agree on an action plan
4. Assist with treatment
5. Arrange follow-up

Management: Lifestyle Modification

The cornerstone component of lipid management is lifestyle modification. In fact, a large systematic review by Iestra et al found that lifestyle choices, such as eating a healthy diet, exercising, and not smoking, were as effective as pharmacologic treatments, such as low-dose aspirin, statins, ace inhibitors, and beta-blockers.[17] For an extensive review of lifestyle modification, refer to the American College of Cardiology/American Heart Association (ACC/AHA) Lifestyle guidelines.[18]

Diet is an important factor in reducing lipid levels and risk for CVD. Since Dr. Ancel Keys linked dietary fats to CVD in the 1960s, there has been a substantial increase in knowledge about the impact of diet. One of the most studied diets is the Mediterranean diet, which appears to be more protective than the standard low-fat diet.[19] The Mediterranean diet promotes the consumption of healthy fats such as olive oil, fish, beans, and nuts. Nuts have been found to be cardioprotective, and patients consuming 1 ounce of nuts seven or more times per week had a 20% lower death rate compared to those who did not eat nuts.[20] Vegetarian or vegan (no animal products at all, including cheese and eggs) diets also have been shown to significantly reduce lipid levels as well as CVD risk. A large meta-analysis of 27 studies demonstrated that plant-based diets significantly reduced LDL-C and triglyceride levels by 8-10 mg/dL. In an interesting comparison study of 34 participants, a vegetarian diet was compared to lovastatin 20 mg a day, and both were compared to a vegetarian diet with almost no dairy (almost vegan). The vegetarian group's LDL dropped 8.5%, the lovastatin group dropped by 33.3%, and the almost vegan diet group's LDL dropped by 29.6%; the lovastatin and almost vegan diet were statistically significantly different from the vegetarian diet but not statistically different from each other.[22] This was accomplished in 1 month's time. It is unclear if these findings persisted or resulted in reduced cardiovascular outcomes, but the study demonstrates that an acute drop in lipids can be achieved through lifestyle modification.

Another study compared the old adage of "an apple a day keeps the doctor away" against statins. Using the British health care system as the basis for their statisical model, researchers compared the impact of placing all patients eligble for primary prevention on an apple a day (with a constant calorie diet) vs generic simvastatin. The model showed that there would be no significant difference in deaths prevented by either strategy — i.e., that an apple a day was just as effective as low-dose generic statin. The major difference was in side effects. In the 17.6 million patients theorectically given statins, there would be an excess of 1200 cases of myalgias, 200 cases of rhabomyolysis, and 12,300 new cases of diabetes.[23] See Table 2 for a summary of these results. This modeling exercise should not be taken to promote the replacement of statins with apples, but highlights the need to discuss the risk/benefit ratio of any treatment with each individual patient.

The AHA recommends behavior change and has published a specific set of guidelines — the 5 A's — to help practitioners start the conversation about lifestyle change and teach patients how to implement behavior change.[24] (*See Table 3*).

Pharmacologic Treatment

Although lifestyle modification is the foundation to treating HLP, very few patients make the recommended lifestyle changes. A recent cross-sectional study of MI and stroke survivors found that only 4.3% made comprehensive lifestyle changes (stopped smoking, changed diet, and started exercising) within 5 years of their event.[25] These numbers necessitate pharmacologic treatment, especially in secondary prevention, in a large percentage of patients.

Statins have been proven to provide significant LDL reductions that coincide with mortality reduction across a large group of secondary and primary prevention patients.[26,27,28,29] Statins have been studied extensively and have an excellent therapeutic window with substantial LDL lowering with a low side effect profile. Typical statin doses and their anticipated effect on LDL are shown in Table 4.[30]

Although there has been much publicity about the side effects of statins, truly dangerous side effects such as liver toxicity and rhabdomyolysis are extremely rare.[31] The recent concerns about increased

Table 4: Statin Effectiveness

High intensity LDL lowering of 50%	Moderate intensity LDL lowering of 30-50%	Low intensity LDL lowering of ~30%
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin 80 mg	
	Pitavastatin 2-4 mg	

cancer risk and cognitive decline are unproven.[32] The two major concerns regarding statins are myalgias and new onset diabetes (as demonstrated in the British health care study; *see Table 2*).

Myalgias affect about 10% of statin users.[31] Furthermore, statins are associated with not only myalgias, but also all other musculoskeletal complaints. These included muscle pain, sprains, strains, dislocations, and arthritis.[33] If the patient complains of any musculoskeletal symptoms with a benign physical exam, it is reasonable to lower the dose, change to another statin, take a statin holiday, or have the patient take a trial of coenzyme Q10 (discussed below). Elevated creatine kinase levels could prove statin-induced muscle involvement if elevated.

One way to test if the statin is causing the myalgias is to give a statin holiday. If the patient is stable from a CVD standpoint, the statin could be held to see if the symptoms resolve. To truly know if the statin had caused the problem, the statin should be reintroduced (Koch's postulate). If the symptoms do not recur, then both the primary care physician and the patient will be reassured and therapy can be continued. This approach has now been studied and published with the name of "n-of-1 experiments."[34]

A provocative trial objectively measured the effect of exercise training with or without statins. Unlike patients randomized to exercise alone, those on statins could not increase their VO_{2max}.[35] Furthermore, it was found that the activity level of citrate synthase, a marker of skeletal muscle mitochondrial content, was decreased by statins but raised by exercise. This could be the mechanism whereby some patients have muscle pain and weakness while on statins.

Although there is a wealth of data suggesting mechanisms for statin-induced myalgias, including lowering serum coenzyme Q10 levels and mitochondrial dysfunction, there are very few good data on the effect of taking supplements to counteract these effects.[31] The best study on this was a double-blind study in humans with muscle symptoms while on statin therapy. Half of the patients received coenzyme Q10 while the other half received a placebo. Both groups reported about a 40% reduction in symptoms.[36] Since this was a small study, clear data are lacking.

Another approach is to try a once-a-week dosing strategy. A small study of patients with statin-induced side effects showed that 74% could tolerate a once-per-week dosing strategy and still had a 23% reduction in LDL-C levels. This study was too small to detect if these changes were enough to affect CVD outcomes, but does offer another option in patients who need to stay on statins but are having significant side effects.[37] From this starting point, it may be reasonable to up titrate statin dose as tolerated by the patient.

Non-statin therapies have not proven as successful as statins in modifying risk. While bile acid sequestrants, niacin, fish oil, fibrates, and ezetimibe lower LDL-C, they are not as powerful as statins, which probably explains their mixed results in outcomes from randomized trials. For this reason, the ACC/AHA Blood Cholesterol Guideline does not recommend any non-statin pharmacologic treatment.

Niacin favorably alters all aspects of the lipid panel. Niacin lowers LDL-C, raises HDL-C, and reduces triglycerides. Niacin was recently studied in the large AIM-HIGH study and found to not alter event rates when used as adjuvant therapy.[38] However, the Coronary Drug Project demonstrated that niacin reduced nonfatal MI, but did not affect mortality. A recent 15-year follow-up of this same study showed a late mortality benefit.[39] Since this benefit occurs after stopping active therapy, it is unclear what, if any, causal relationship exists. An interesting meta-analysis demonstrated a protective effect of niacin on major cardiovascular events that was independent of the on-treatment HDL-C level.[40] A possible mechanism for this non-HDL-C effect was demonstrated in a small retrospective study of the HATS and FATS trials. Niacin had the predicted effect on routine lipid parameters, but also altered the lipoprotein particle density distribution that correlated to angiographic and clinical results.[41] So while it is difficult to titrate niacin up to an effective dose due to flushing and gastrointestinal upset, consideration of using niacin can be reserved in patients where the lipid profile is not well controlled and the patient does not tolerate doses of statins appropriate to their level of risk.

Fish oil has also been studied extensively. Early studies showed that it was indeed effective in lowering triglyceride levels, and that it also appeared to be effective in reducing arrhythmias and even sudden cardiac death.[42] This study was even more impressive as it was done in a Japanese population with

a high background of fish intake. Two recent well-designed, large-scale, double-blind, randomized, controlled studies have now demonstrated that fish oil, while lowering triglycerides, had no impact on CVD event rates or death.[43] One of these studies was done in diabetic patients, a high-risk group that would receive the most benefit.[44] At this point, it is not recommended to use fish oil for the prevention of heart disease. The large GISSI-Prevenzione study showed a reduction in cardiovascular endpoints, including mortality, in a secondary prevention population.[45] However, fish oil may still be useful in patients with CVD who have serum triglycerides > 500 mg/dL.

Fibrates have a mixed picture as well. Some early trials such as VA-HIT showed a benefit for gemfibrozil in preventing cardiovascular events in men with established coronary artery disease.[46] In the FIELD trial (both primary and secondary prevention) among patients with low HDL-C and high triglycerides, fenofibrate conferred a 27% reduction in the primary composite endpoint.[47] The recent ACCORD study in diabetics did not show any benefit of adding fibrates to simvastatin in affecting outcomes.[48] However, there seemed to be a benefit in the low-HDL/high-triglyceride group that, coupled with the results of the FIELD study, suggests fibrates may be helpful in patients with this lipid phenotype. Gemfibrozil should not be used in combination with a statin because it can reduce statin elimination and increase risk for rhabdomyolysis.[49]

Ezetimibe reduces LDL-C by 20% by blocking the absorption of cholesterol from the gastrointestinal tract. It is typically used as adjunctive therapy with statins to achieve greater LDL reduction. There is controversy over its role (if any), as there are currently no good clinical outcomes studies with ezetimibe. In the ENHANCE trial, when ezetimibe was added to simvastatin, it did not significantly reduce carotid intima-media thickness (CIMT).[50] However, in the smaller SANDS and VYCTOR trials, it did contribute to CIMT regression.[51,52] When compared head to head with niacin, it performed worse in the ARBITER 6-HALTS study on CIMT regression.[53]

In the SHARP trial, the combination of simvastatin/ezetimibe reduced the risk for the primary composite endpoint in patients with chronic kidney disease.[54] In this study, risk reduction was proportional to magnitude of LDL-C reduction. In the SEAS trial, simvastatin/ezetimibe therapy reduced the risk for ischemic cardiac events.[55] However, both of these studies tested the combination of statin and ezetimibe against placebo and could not measure the effect of ezetimibe beyond that of the statin. The IMPROVE-IT trial (ClinicalTrials.gov # NCT00202878) is evaluating the impact of adjuvant ezetimibe in patients post-ACS. The study is completed and will be presented later this year. Until those results are known, ezetimibe is a reasonable option for those with high residual LDL or as lone therapy in truly statin-intolerant patients.

Controversies: HDL

While most of the discussion has focused on LDL-C lowering, what about HDL-C? HDL-C level has been shown to be a "protective," negative risk factor for CVD.[56] This has led to several attempts to raise HDL pharmacologically. The first attempt was with the cholesteryl ester transfer protein (CETP) torcetrapib. This approach has met with failure due to increased death rates possibly related to increased blood pressure, electrolyte disturbances, and other off-target toxicities.[57] A similar compound, dalcetrapib, did not increase mortality, but while it raised HDL-C levels, there was no reduction in cardiovascular events.[58]

The absolute HDL-C level may not be the most important feature of HDL. HDL efflux capacity (measured at the cell level) is more predictive of the degree of CIMT than the actual HDL level itself.[59] Furthermore, studies in a population from a small village in rural Italy without any significant CVD and enhanced longevity found that they had very low HDL levels.[60] These villagers carried a mutation known as ApoA-1 Milano. Using recombinant ApoA-1 Milano infused weekly into human subjects, intravascular ultrasound demonstrated plaque regression in as little as 5 weeks.[61] It appears that the functionality rather than the amount of HDL-C determines benefit.

Probably the most important new data regarding HDL have come from a large-scale genetic study. Researchers evaluated single-nucleotide polymorphisms (SNPs) associated with HDL (using SNPs associated with LDL as a control) and then looked for relationships with clinical disease. As expected, the SNPs associated with low LDL were protective while the SNPs associated with high LDL led to higher prevalence of disease. More interestingly, no HDL SNP had any predictive value on disease status.[62] At this point, most researchers believe HDL is at best a surrogate marker for some other process that tracks with it, but it is not causative in and of itself. At present, the HDL hypothesis awaits definitive confirmation.

Confusion and Controversy Around the New ACC/AHA Guidelines

The ACC/AHA published new guidelines for the treatment of lipids in November 2013.[30] The ACC and AHA did a systematic evidence review of RCTs for statins and found a consistent reduction in atherosclerotic cardiovascular disease (ASCVD) events in primary and secondary prevention populations, with the exception of ASCVD event reduction in those with New York Heart Association class II-IV heart failure and those receiving hemodialysis. The RCTs reviewed by the ACC/AHA either compared fixed doses of statins with placebo or untreated controls, or compared fixed doses of higher-intensity statins with moderate-intensity statins. These trials were not designed to evaluate the effect of dose-adjusted statin treatment

Table 5: Four Statin Recommended Treatment Groups

1. Individuals with clinical ASCVD
2. Individuals with primary elevations of LDL–C ≥ 190 mg/dL
3. Individuals 40-75 years of age with diabetes and LDL-C 70-189 mg/dL
4. Individuals 40-75 years of age without clinical ASCVD or diabetes with LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher

to achieve LDL-C or non-HDL-C goals; hence, no recommendations were given to titrate cholesterol-lowering drug therapy to achieve LDL-C or non-HDL-C goals as recommended by ATP III. The expert panel recommended as per RCTs that statins should be used in those populations most likely to benefit with high-intensity vs moderate-intensity therapy. The recommended treatment groups in the new lipid guidelines are shown in Table 5.

The new ACC/AHA lipid guidelines have generated significant controversy as well as confusion focused on two new points discussed in detail below.

No More Focus on Actual LDL Levels

The new guidelines are based on interpreting what was actually demonstrated in the statin trials. All of the major statin trials tested a strategy of high-dose statin vs lower-dose statin or placebo and not necessarily treating to a target LDL-C level. While this may be factually true, it may be conceptually wrong. Although it is true that the specific hypothesis tested in the various statin trials was not a targeted LDL goal, it is clear that LDL-C level is predictive of risk and that patients who achieved a lower LDL level had adverse cardiovascular events.

There is significant evidence from both predictive models and in a regression analysis that LDL-C levels matter. Using a regression model approach, it has been estimated that a patient would have to have the LDL-C lowered to 55 to achieve a 0% event rate and to 30 in secondary prevention.[63] In the same article, a regression model looking at all the quantitative angiography and intravascular ultrasound data demonstrated that to stop the loss of coronary arterial minimal lumen diameter, the LDL-C would have to be decreased to 70. Probably the most influential acute care statin study is TIMI 22-Prove IT, which studied high-dose atorvastatin against standard dose pravastatin.[28] In that study, atorvastatin was superior to pravastatin in reducing cardiac events. While the atorvastatin arm was what is now called a "high-intensity" treatment vs a "moderate intensity" treatment (pravastatin), the obvious difference was achieved LDL-C levels. The average achieved LDL-C was 62 in the atorvastatin arm and 95 in the pravastatin arm. This has been borne out in all the other studies of statins. While the initial hypothesis was not to reach a target LDL, the improvement in event rates paralleled the achieved LDL-C level. Moreover, in an important post-hoc analysis of PROVE-IT, attaining an LDL-C of < 40 compared to 80-100 mg/dL was associated with a significant 39% incremental risk reduction for cardiovascular events.[64]

Furthermore, the new guidelines use hard LDL values multiple times. They recommend no treatment if the LDL-C is already under 70. They also recommend starting treatment if the LDL is > 190. Finally, non-HDL (or LDL) is used in the new risk calculator. It is clear that even though the new guidelines want to de-emphasize LDL-C, it still matters.

Finally with the recent loss of enthusiasm for modifying HDL and lack of benefit modifying triglyceride levels, it leaves only the LDL-C as a therapeutic target. As the lone remaining lipid target, it makes sense to try and optimize its level.

Pooled Cohort Equations Risk Calculator

Even more controversial than the decision to abandon LDL targets is the new risk calculator (*see Table 6*). The new set point for considering starting statin therapy is a 7.5% risk over 10 years as determined by the risk calculator. This is a change from the old risk scoring in the Framingham Risk Score (FRS). By the old FRS, high risk was a 20% risk over 10 years and moderate risk was 10-20% over 10 years. The annual risk now considered to be high risk has been reduced from 2.0% per year to 0.75% per year. This represents a significant change and potential increase in statin usage. The authors fully admit that choosing the 7.5% risk level is arbitrary, but also point out that choosing any level, including the old 20% risk level is arbitrary as well. The appropriate risk/benefit ratio will have to be determined on an individual basis with each patient and his/her physician.

Ridker applied the new risk calculator to several clinical trial populations and found that it overestimates risk by about two-fold.[65] The estimated impact on the United States would be an additional 12.8 million people eligible for statin therapy.[66] These 56 million total patients would represent 48.6% of the entire 40-75 age group in the United States. This push has been coined the "statinization" of America.[67] Probably the most important "side effect" of the new risk calculator is that it will stimulate discussion between doctors and patients about their lipids levels and how best to address it through lifestyle change and/or statins.

Recommended Treatment Algorithm

1. Assess patient risk level and measure fasting lipid profile.

2. If patient is in one of the first three out of four high-risk groups (*see Table 5*) or has an LDL > 160, advise lifestyle change and discuss possible statin therapy.

If the patient has a risk greater than 7.5% by the Pooled Cohort Risk Calculator, discuss with the

Table 6: Examples of Risk Calculator

Risk Factors	Units	Enter Patient's Values in this Column	Acceptable Ranges of Values	Optimal Values
Sex	M (for males) or F (for females)		M or F	
Age	Years		20-79	
Race	AA (for African American) or WH (for white and others)		AA or WH	
Total Cholesterol	mg/dL		120-320	170
HDL Cholesterol	mg/dL		20-100	50
Systolic Bood Pressure	mmHg		90-200	110
Treatment of High Blood Pressure	Y (for yes) or N (for No)		Y or N	N
Diabetes	Y (for yes) or N (for No)		Y or N	N
Smoker	Y (for yes) or N (for No)		Y or N	N

A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx.[53]

patient both your and the patient's level of comfort with starting any treatment at a specific risk level. The appropriate risk/benefit ratio will have to be determined on an individual basis with each patient and his/her own doctor and not at an arbitrary threshold value.

3. Reassess response to treatment plan. Repeat LDL measurement and check for side effects. Set goal LDL of < 100 in stable patients and < 70 for higher-risk patients.

4. If residual LDL is still high after maximum tolerated statin dose, consider adding ezetimibe.

5. If patient is a secondary prevention patient or in a high-risk group but truly cannot tolerate statins, consider monotherapy with fibrate (first option especially in patients with low HDL-C and high triglycerides), ezetimibe (second option), or niacin (third option).

Summary

LDL-C is a powerful predictive and pathogenic factor in CVD and mortality. All adult patients should be assessed for not only elevated LDL-C levels, but also overall risk. Lifestyle change should be the foundation of any therapeutic treatment plan addressing lipids. Statin therapy directed at lowering the LDL-C has been shown to be protective and is first-line pharmacotherapy. Ezetimibe may be added for patients not achieving significant reductions on statins alone. For statin intolerant patients, niacin, ezetimibe, or fibrates may be useful and should be considered as monotherapy until more data are available. The new Pooled Cohort Equations Risk Calculator may overestimate risk, but does serve as a good starting point for discussing risk/benefit ratios of treatment with individual patients.

References

1. Genet J, Libby P. Lipoprotein disorders and cardiovascular disease. In: *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 8th edition. Bonow R, et al, eds. Philadelphia: Saunder Elsevier; 2008:1071-1091.
2. Avrum IG. Blood vessels. In: *Rubin's Pathology*. 4th edition. Rubin R, et al, eds. Baltimore: Lipincott Williams and Wilkins; 2005:493-498.
3. McQueen MJ, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarctions in 52 countries (the INTERHEART study): A case-control study. *Lancet* 2008;372:224-233.
4. Carroll MD, et al. Trends in serum lipids and lipoproteins of adults, 1960-2002. *JAMA* 2005;294:1773-1781.
5. Capewell S, et al. Life-years gained among US adults from modern treatments and changes in the prevalence of 6 coronary heart disease risk factors between 1980 and 2000. *Am J Epidemiol* 2009;170:229-236.
6. World Health Organization. Global Database on Body Mass Index. Available at: http://apps.who.int/bmi/index.jsp. Accessed May 16, 2014.
7. Centers for Disease Control and Prevention. Overweight and Obesity. Available at: http://www.cdc.gov/obesity/childhood/index.html. Accessed May 16, 2014.
8. Albert KG, et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society;

and International Association for the Study of Obesity. *Circulation* 2009;120:1640-1645.
9. Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006. *Natl Health Stat Report* 2009;13:1-7.
10. McCullough AJ. Epidemiology of the metabolic syndrome in the USA. *J Dig Dis* 2011;12:333-340.
11. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med* 2013;368:2004-2013.
12. Gloy VL, et al. Bariatric surgery versus non-surgical treatment for obesity: A systematic review and meta-analysis of randomized controlled trials. *BMJ* 2013;347:f5934.
13. Rader DJ, Hobbs HH. Disorders of Lipoprotein Metabolism. In: *Harrison's Principles of Internal Medicine*. 16th edition. Kasper D, et al, eds. New York: McGraw Hill Professional-Publisher; 2005:2286-2297.
14. Langsted A, et al. Fasting and nonfasting lipid levels: Influence of normal food intake on lipids, lipoprotein, apolipoprotein, and cardiovascular risk prediction. *Circulation* 2008;118:2047-2056.
15. Nigam PK. Serum lipid profile: Fasting or non-fasting? *Indian J Clin Biochem* 2011;26:96-97.
16. 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 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421.
17. Iestra JA, et al. Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: A systematic review. *Circulation* 2005;112:924-934.
18. Eckel RH, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *Circulation* 2013 Nov. 12 [Epub ahead of print].
19. Estruch R, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279-1290.
20. BaoY, et al. Association of nut Consumption with total and cause-specific mortality. *N Engl J Med* 2013;369:2001-2011.
21. Ferdowsian HR, Barnard ND. Effects of plant-based diets on plasma lipids. *Am J Cardiol* 2009;104:947-956.
22. Jenkins DJ, et al. Direct comparison of a dietary portfolio of cholesterol-lowering foods with a statin in hypercholesterolemic participants. *Am J Clin Nutr* 2005;81:380-387.
23. Briggs A, et al. A statin a day keeps the doctor away: Comparative proverb assessment modelling study. *BMJ* 2013;347:f7267.
24. Spring B, et al. Better population health through behavior change in adults: A call to action. *Circulation* 2013;128:2169-2176.
25. Teo K, et al. Prevalence of a healthy lifestyle among individuals with cardiovascular disease in high-, middle- and low-income countries: The Prospective Urban Rural Epidemiology (PURE) study. *JAMA* 2013;309:1613-1621.
26. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-1389.
27. Shepherd J, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301-1307.
28. Cannon CP, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-1504.
29. Ridker PM, et al; JUPITER study group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195-2207.
30. Stone NJ, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013 Nov. 7. doi: 10.1016/j.jacc.2013.11.002 [Epub ahead of print].
31. Pasternak RC, et al. ACC/AHA/NHLBI clinical advisory on use and safety of statins. *J Am Coll Cardiol* 2002;40:567-572.
32. Jukema JW, et al. The controversies of statin therapy: Weighing the evidence. *J Am Coll Cardiol* 2012;60:875-881.
33. Mansi I, et al. Statins and musculoskeletal conditions, arthropathies, and injuries. *JAMA Intern Med* 2013;173:1-10.
34. Joy TR, et al. N-of-1 (single patient) trials for statin-related myalgia. *Ann Intern Med* 2014;160:301-310.
35. Mikus CR, et al. Simvastatin impairs exercise training adaptations. *J Am Coll Cardiol* 2013;62:709-714.
36. Bookstaver DA, et al. Effect of coenzyme Q10 on statin-induced myalgias. *Am J Cardiol* 2012;110:526-529.
37. Ruisinger JF, et al. Once-a-week rosuvastatin (2.5 to 20 mg) in patients with a previous statin intolerance. *Am J Cardiol* 2009;103:393-394.
38. AIM-HIGH Investigators, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255-2267.
39. Canner PL, et al. Fifteen year mortality in Coronary Drug Project patients: Long-term benefit with niacin. *J Am Coll Cardiol* 1986;8:1245-1255.
40. Lavigne PM, Karas RH. The current state of niacin in cardiovascular disease prevention: A systematic review and meta-regression. *J Am Coll Cardiol* 2013;61:440-446.
41. Zambon A, et al. Effects of niacin combination therapy with statin or bile acid resin on lipotroteins and cardiovascular disease. *Am J Cardiol* 2014;113:1494-1498.
42. Iso H, et al. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: The Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation* 2006;113:195-202.
43. Risk and Prevention Study Collaborative Group, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med* 2013;368:1800-1808.
44. ORIGIN Trial Investigators, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med* 2012;367:309-318.
45. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction:

results of the GISSI-Prevenzione trial. *Lancet* 1999;354: 447-455.
46. Robins SJ, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: A randomized controlled trial. *JAMA* 2001;285:1585-1591.
47. FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. *Lancet* 2005;366:1849-1861.
48. Ginsberg HN, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563-1574.
49. Pasternak RC, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-572.
50. Kastelein JJ, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;358:1431-1443.
51. Fleg JL, et al. Effect of statins alone versus statins plus ezetibmie on carotid atherosclerosis in type 2 diabetes: The SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. *J Am Coll Cardiol* 2008;52:2198-2205.
52. Farmer J. The Vytorin on carotid-media thickness and overall arterial reigiity (VYCTOR) study. *Expert Rev Cardiovasc Ther* 2009;7:1057-1060.
53. Villines TC, et al. The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis): Final results and the impact of medication adherence, dose, and treatment duration. *J Am Coll Cardiol* 2010;55:2721-2726.
54. Baigent C, et al; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): A randomised placebo-controlled trial. *Lancet* 2011;377:2181-2192.
55. Holme I, et al. Observed and predicted reduction of ischemic cardiovascular events in the Simvastatin and Ezetimibe in Aortic Stenosis trial. *Am J Cardiol* 2010;105:1802-1808.
56. Assmann G, et al. Atherosclerosis: Evolving vascular biology and clinical implications. HDL cholesterol and protective factors in atherosclerosis. *Circulation* 2004;109:III-8-III-14.
57. Barter PJ, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;357:2109-2122.
58. Schwartz GG, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;367:2089-2099.
59. Khera AV, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* 2011;364:127-135.
60. Gualandri V, et al. AlMilano apoprotien identification of the complete kindred and evidence of a dominant genetic transmission. *Am J Hum Genet* 1985;37:1083-1097.
61. Nissen SE, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: A randomized controlled trial. *JAMA* 2003;290:2292-2300.
62. Voight BF, et al. Plasma HDL cholesterol and risk of myocardial infarction: A mendelian randomisation study. *Lancet* 2012;380:572-580.
63. O'Keefe JH Jr, et al. Optimal low-density lipoprotein is 50 to 70 mg/dl: Lower is better and physiologically normal. *J Am Coll Cardiol* 2004;43:2142-2146.
64. Wiviott SD, et al; PROVE IT-TIMI 22 Investigators. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: A PROVE IT-TIMI 22 substudy. *J Am Coll Cardiol* 2005;46:1411-1416.
65. Ridker PM, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;352:20-28.
66. Ridker PM, Cook NR. Statins: New American guidelines for prevention of cardiovascular disease. *Lancet* 2013;382:1762-1765.
67. Pencina MJ, et al. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med* 2014;370:1422-1431.
68. Ioannidis JP. More than a billion people taking statins? Potential implications of the new cardiovascular guidelines. *JAMA* 2014;311:463-464.

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CME questions

1. What percentage of myocardial infarction and stroke survivors make comprehensive lifestyle changes?
   a. > 75%
   b. > 50%
   c. > 25%
   d. < 5%
2. A patient with history of myocardial infarction, type 2 diabets, and hyperlipidemia experiences myalgias after starting atorvastatin. Which of the following would be a reasonable step in management of hyperlipidemia?
   a. Lower the dose of atorvastatin
   b. Change to another statin
   c. Statin "holiday"
   d. Trial of coenzyme Q10
   e. All of the above
3. Which of the following is ***not*** an indication for statin therapy under the new ACC/AHA 2013 guidelines of hyperlipidemia management?
   a. Individuals with clinical ASCVD
   b. Individuals with primary elevations of LDL-C ≥ 190 mg/dL
   c. Individuals 40-75 years of age with diabetes and LDL-C 70-189 mg/dL
   d. Individuals 40-75 years of age without clinical ASCVD or diabetes with LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of 5% or higher
4. What percentage of the U.S. population is overweight or obese?
   a. 50-55%
   b. 55-60%
   c. 60-65%
   d. 65-70%
5. Metabolic syndrome is defined by all of the following criteria *except*:
   a. central obesity (waist circumference ≥ 102 cm in men and ≥ 88 cm in women).
   b. HTN (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or drug treatment for HTN).
   c. decreased HDL (< 40 mg/dL in men and < 50 mg/dL in women, or drug therapy for reduced HDL).
   d. elevated triglycerides (≥ 200 mg/dL, or drug treatment for elevated triglycerides).
   e. insulin resistance (fasting plasma glucose ≥ 100 mg/dL, or therapy for hyperglycemia).
6. All of the following are examples of pleiotropic effects of statins *except*:
   a. reduced inflammation.
   b. increased levels of interstitial collagen.
   c. increased expression of interstitial collagenase (MMP-1).
   d. lower levels of oxidized LDL.
   e. reduced production of reactive oxygen species.
7. A 55-year-old white male with history of type 2 diabetes, hypertension, and myocardial infarction complains of myalgias while taking atorvastatin. After atorvastatin is stopped, myalgias seem to improve. Which of the following next step in management would be consistent with the "n of 1" study concept?
   a. Restart atorvastatin and monitor for myalgias
   b. Avoid further use of any statins in this patient due to myalgias
   c. Start the patient on niacin
   d. Start the patient on ezetimibe

In Future Issues: Rheumatoid Arthritis

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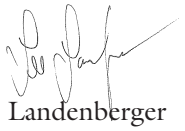

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