

An Update on Statin Alternatives and Adjuncts

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Abstract and Introduction

Abstract

LDL cholesterol is the primary target of therapy to lower cardiovascular risk. Statins are medications of first choice to lower LDL cholesterol, but cannot be tolerated in up to 10% of individuals. Intermittent dosing strategies for statins can help reduce muscle symptoms in some patients. A Mediterranean-type diet supplemented with plant stanols and sterols, fiber and fish oils can help achieve cholesterol goals and reduce cardiovascular events. Caution may be needed when using supplements, such as red yeast rice, because of the concern regarding contaminants. Other lipid-lowering medications, such as intestinal agents, niacin and fibrates, can be used as alternative strategies in patients who cannot tolerate statins or in combination with low-dose statins to achieve lipid goals and reduce cardiovascular risk.

Introduction

The recognition and treatment of coronary risk factors, such as dyslipidemia, has made a substantial impact on reducing coronary heart disease events. The National Cholesterol Education Program (NCEP) guidelines recommend LDL cholesterol (LDL-C) as the primary target of therapy to reduce cardiovascular events. The HMG-CoA reductase inhibitors or statins are effective in lowering LDL-C and are considered drugs of first choice for treating dyslipidemias. Not everyone, however, can tolerate statins, necessitating different strategies to lower LDL-C in these individuals.

There are currently seven statins available in the US market. The statins differ in terms of efficacy, half-life, metabolism, drug–drug interactions and potential for side effects. All are effective LDL-C-lowering drugs by inhibiting the enzyme that catalyzes the rate-limiting step in cholesterol synthesis. This leads to clearance of LDL-C particles from the circulation by the liver.

The major adverse effect of statins is the potential for liver and muscle toxicity. All statins can cause hepatotoxicity or myopathy. Hepatotoxicity is defined as an elevation in liver transaminases (alanine aminotransferase

and/or aspartate aminotransferase) over three-times the upper limit of normal. Hepatotoxicity occurs in <1% of patients with standard doses of statins.^[1] The prevalence of hepatotoxicity may be higher with full doses of the more potent statins. An increase in liver transaminases in the absence of an increase in bilirubin has not been linked with definite liver injury. If the liver enzymes become greater than three-times the upper limit of normal, statin use can be discontinued and the transaminases usually return to normal. At times, lower doses of statins can be used without increasing the enzymes to the toxicity range. Statins should not be used in patients with advanced liver disease since the systemic exposure to the drug can be significantly increased in these patients.

Myopathy can be divided into three categories: myalgias, myositis and rhabdomyolysis. Myalgias are described as a soreness, tenderness or weakness of muscles, either at rest or brought on by exertion. Enzyme abnormalities are usually not present in patients presenting with myalgias. The incidence of myalgias is reported to be approximately 5% in randomized clinical studies, but surveys of longer-term use suggest that myalgias may be experienced by >10% of patients.^[2] Myalgias are the most common adverse effect causing discontinuation of statins.

Myositis is defined as an increase in creatine kinase (CK) greater than ten-times the upper limit of normal and may or may not be associated with myalgia symptoms. The incidence of myositis is less than one case per 10,000 patients per year with standard dose statins, but may be higher with higher-dose treatments, such as 80 mg simvastatin daily or in cases of drug–drug interactions.^[3]

Rhabdomyolysis is severe myopathy involving muscle breakdown and release of myoglobin into the circulation. If the muscle damage is extensive, renal damage can occur. The National Lipid Association has defined rhabdomyolysis as a CK of >10,000 IU/l or a CK >ten-times the upper limit of normal, plus evidence for worsening renal function.^[4] This is a very rare adverse reaction with these agents and is more likely to occur if there is a drug–drug interaction causing systemic accumulation of the drug.

Use of Statins in Patients With Myalgias

Myalgias are the most common adverse effect causing discontinuation of statins. Before abandoning statin therapy, it is important to determine if muscle complaints are due to the statin medication. It is useful to obtain a muscle and joint pain history prior to prescribing a statin. Subsequent muscle complaints can then be compared with the initial report to

determine if new symptoms have developed. Many patients complain of joint aches, which are unlikely to be due to the statin. Likewise, muscle cramps, especially cramping in the legs that typically occur at night, are not likely due to the statin drugs. A drug-free holiday for a few weeks followed by reintroduction of the statin can be an effective way to determine if the muscle complaints are likely to be due to the statin medication.

Changing statin types may improve tolerability of the statins. A statin metabolized by a different enzymatic system may be better tolerated. Lovastatin, simvastatin and atorvastatin are metabolized by the CYP450 3A4 system in the liver, whereas pravastatin, rosuvastatin and pitivastatin are metabolized by alternate pathways. Choosing a statin that has a different mechanism of metabolism, especially if other medications are being used that utilize the same metabolic pathways, may lead to reduced muscle symptoms. The hydrophilicity or lipophilicity of statins may correlate with muscle symptoms. Highly lipophilic statins, such as simvastatin and lovastatin, may increase the risk for CK elevations compared with low lipophilic statins, such as pravastatin and rosuvastatin.^[5] Finally, genome-wide association studies have identified a strong association of myopathy with a single nucleotide polymorphism, suggesting that genetic variation in the population may be linked to the risk of myopathy.^[6] Genotyping of patients may prove useful in identifying individuals at the highest risk of toxicity.

Intermittent Statin Dosing

The newer statins on the market have longer half-lives than the original statins. Alternative dosing schedules using once-, twice- or three-times a week or every-other-day dosing, have been investigated as methods to reduce myalgias and yet achieve efficacy in lowering LDL-C. Rosuvastatin with a 19-h half-life and atorvastatin with an 11–24-h half-life (parent drug and active metabolite) are particularly useful for this approach.

A pilot study using every-other-day atorvastatin dosing showed comparable LDL-C-lowering efficacy with daily dosing, although the doses used on an every-other-day schedule were higher than the daily dose needed to achieve the same degree of LDL-C lowering.^[7] A prospective trial of once-a-week rosuvastatin dosing in individuals with a history of myalgias on statin therapy achieved a >12% lowering of LDL-C and 80% of the patients were able to continue the medication without experiencing myalgias.^[8] A retrospective investigation of patients that were not able to tolerate statins determined that over 72% of individuals were able to tolerate an every-other-day regimen of a low dose of rosuvastatin with a mean LDL-C reduction of approximately 34%.^[9] There are no outcome

studies performed with intermittent dosing of statins so it is not known if this treatment approach will give the same degree of event reduction for the LDL-C level as achieved with daily dosing.

Combination therapy with a statin plus an intestinal agent can be used in individuals that can only tolerate a low-dose statin or an intermittent dosing of the statin. The combination of a statin with ezetimibe or with a resin, such as colesevelam, can achieve an additional 20% LDL-C reduction.^[10] Since the intestinal agents do not have systemic exposure, they would not be expected to worsen myalgias.

Dietary Approach

A correlation between the intake of dietary fat and the incidence of coronary heart disease has been observed in multiple population studies.^[11] Very low-fat diets have been advocated to lower serum cholesterol levels. A very low-fat diet is defined as a diet in which $\leq 15\%$ of total calories are derived from fat. This would correlate to 33 g of fat for a 2000 calorie diet. Adhering to a very low-fat diet has been shown to reduce LDL-C by 10–20%.^[12] The reduction in LDL-C is attributed to a decrease in saturated fat in the diet. Most very low-fat diets are vegetarian-type diets.

The Lifestyle Heart Trial combined a very low-fat diet (10% fat) with intensive lifestyle changes, including aerobic exercise, stress management, smoking cessation and group psychosocial support for 5 years, in selected individuals with coronary artery disease.^[13] At 1 year, LDL-C decreased by 40%. In addition, the study documented more regression of coronary atherosclerosis and fewer clinical cardiovascular events in the very low-fat group compared with a control group of patients.

Adherence to a very low-fat diet can be difficult for most patients. The NCEP Adult Treatment Panel III has advocated a normal-fat diet (25–35% of total calories), but with reduced saturated fats of $<7\%$ of calories and of cholesterol <200 mg/day.^[14] In addition, it was recommended to enhance LDL-C lowering by adding 2 g/day of plant stanols and sterols, and increasing soluble fiber to 10–25 g/day.

The Portfolio diet studies were designed to determine whether a diet containing all the recommended food components by the NCEP can significantly lower LDL-C. The Portfolio diet is a vegetarian-type diet. The initial study randomized 46 hyperlipidemic individuals to either a low-saturated fat diet (control), the same diet plus lovastatin 20 mg/day (statin) or a Portfolio diet – high in plant sterols (1 g/1000 kcal) soy protein (21.4 g/1000 kcal), soluble fiber (9.8 g/1000 kcal) and almonds (14 g/1000

kcal).^[15] During the 4-week study period, the diets were provided to the participants. The control, statin and portfolio-diet groups had a mean LDL-C reduction of 8.0, 30.9 and 28.6%, respectively. This study suggested that adherence to the NCEP therapeutic lifestyle diet can achieve the same degree of LDL-C lowering as using a starting-dose statin medication.

Patients using a dietary approach to lipid lowering can have difficulty maintaining ongoing strict adherence to the diet. The Portfolio study group followed-up the original study with a 6-month dietary advice study of 351 participants instead of a protocol where the diet was given to the individuals.^[16] The participants in the study received dietary advice regarding a low-saturated fat diet (control) or the portfolio diet, emphasizing the incorporation of plant sterols, soy protein, soluble fiber and nuts into the diet. LDL-C reductions were 13.8% for the portfolio diet compared with 3.0% for the control diet. More frequent dietary advice to a subset of participants did not achieve further LDL-C reduction. Although this study showed that dietary advice over a 6-month period can achieve a significant reduction in LDL-C, the degree of lipid lowering is less than can be expected with a statin medication.

Dietary therapy can be useful as adjunctive therapy to medication. The combination of a low-dose or an intermittent dosing statin, and strict adherence to a low-saturated fat diet, may allow patients to achieve their LDL-C goals, while limiting toxicity from the drug therapy. The combination of a very low-fat diet (Pritikin diet with <10% calories from total fat) with background statin therapy added an additional 19% total cholesterol reduction on top of the 20% reduction already achieved by the statin therapy.^[17]

The portfolio diet added soy protein as the major protein source, replacing animal protein in the diet. A number of studies suggest that replacing animal protein with soy protein can reduce LDL-C and total cholesterol. A meta-analysis of 38 controlled clinical trials indicated that an average soy protein intake of 47 g/day lowered total cholesterol by approximately 9% and LDL-C 13%.^[18]

Plant Stanols & Sterols

Foods that contain plant stanol or sterols can lower cholesterol levels. Over 40 different phytosterols have been identified with sitosterol, campesterol and stigmasterol the most common in food sources. Stanols are saturated sterols. Foods that are enriched with plant stanols or sterols lower serum cholesterol levels by reducing intestinal absorption of cholesterol. The stanols and sterols displace cholesterol from micelles in

the intestine and may interact with an enterocyte pathway that pumps sterols out of the cell, therefore preventing uptake of the cholesterol-containing micelles.^[19] A summary of 55 randomized placebo-controlled trials showed that approximately 2 g/day of plant stanols and sterols reduces LDL-C by approximately 10%.^[20] The reduction in LDL-C can be additive to a low-saturated fat diet or medical therapy. The efficacy in LDL-C reduction seems to be the same if stanols and sterols are taken once a day or in divided servings.^[20] The addition of sterols and stanols to statin therapy can achieve an additive LDL-lowering effect. A study of 167 individuals on statin therapy reported an additional 10% lowering of LDL when a stanol ester margarine was added to the diet.^[21]

The addition of nuts to the diet may also help reduce LDL-C levels. Nuts are rich in plant protein, fiber, phytosterols and unsaturated fatty acids. A pooled analysis of 25 nut consumption trials showed that a mean daily consumption of 67 g of nuts reduced LDL-C by 7.4%.^[22] The effect of nut consumption was dose related and different types of nuts had a similar efficacy. Walnuts may be particularly helpful because they contain the ω -3 fat, α -linolenic acid that may give an additional benefit in reducing cardiac events. Epidemiologic studies have suggested that a diet high in nuts is associated with lower coronary heart disease events.^[23–25]

Soluble Fiber

Dietary fiber has been shown to decrease serum total cholesterol and LDL-C levels. Dietary fiber may also help improve glycemic control and reduce the risk of developing Type II diabetes. Dietary fiber can be classified into two groups depending on its solubility in water. Soluble fiber includes oats, flaxseed, barley, psyllium and pectin. Insoluble fibers include cellulose, lignins and wheat bran. Soluble fibers bind bile acids in the intestine causing increased elimination of the bile salts. This leads to upregulation of bile acid synthesis in the liver. Since cholesterol is an integral component of bile acid synthesis, there is an upregulation of hepatic LDL receptors and increased LDL-C clearance from the circulation. Insoluble fiber does not have the same effect on reducing LDL-C unless it replaces saturated fat in the diet. A meta-analysis of 67 trials showed that ingestion of 2–10 g/day of soluble fiber in the diet can reduce LDL-C by approximately 7%.^[26] Adding soluble fiber to statin therapy can achieve a similar LDL-C-lowering effect as in doubling the statin dose. One study showed that adding psyllium fiber to 10 mg simvastatin/day achieved a similar LDL-C reduction to that achieved with 20 mg simvastatin/day.^[27] This strategy may help individuals who can only tolerate a low dose statin achieve their LDL goal.

Epidemiologic studies have suggested that a diet high in dietary fiber is

associated with a lower incidence of coronary heart disease events. The National Health and Examination Survey showed an inverse relationship between legume and soluble fiber intake, and the risk of coronary heart disease.^[28,29] Legumes are high in bean protein and soluble fiber. A 12% lower risk of coronary heart disease was noted for individuals with a mean intake of approximately 22 g/day of soluble fiber. A meta-analysis of ten prospective cohort studies was performed to evaluate the association between dietary fiber and coronary heart diseases.^[30] The consumption of dietary fiber from cereals and fruits was inversely associated with the risk of coronary heart disease, with a 10–30% lower risk for each 10 g/day increment of fiber.

Fish Oils

Treatment with fish oils for the prevention of cardiovascular events has been supported by a number of clinical trials. The GISSI-Prevenzione trial randomly assigned over 11,000 postmyocardial infarction patients to receive 1 g/day of marine fish oils and showed a 15% reduction in the composite primary end point of death, nonfatal myocardial infarction or nonfatal stroke.^[31] In addition, there was a 45% reduction in the rate of sudden death suggesting that marine fish oils may have an anti-arrhythmic effect in ischemic heart disease patients. Since the publication of GISSI-Prevenzione, additional studies have shown conflicting results. A recent meta-analysis of 20 studies showed no statistically significant association with fish oils and cardiovascular outcomes.^[32] The authors pointed out, however, that strong significant effects of fish oils were seen in earlier studies, but these results were not reproduced in studies reported over the last 5 years. One potential explanation for this finding is the difference in cointerventions in the more recent studies. Current studies have a higher percentage of individuals taking optimal medical management, including statin therapy, which may have brought about significant risk reduction that cannot be further modified by the addition of fish oils. In patients that cannot take statins, however, the benefit of fish oils may approach what was observed in the earlier era studies at a time when patients were not receiving what is now considered optimal medical care.

The addition of ω -3 fish oils to the diet can lower triglyceride levels. Marine-based ω -3 fatty acids (eicosapentenoic acid and docosahexenoic acid) are more effective in lowering triglycerides than plant-derived oils. A meta-analysis of numerous fish oil trials concluded that ω -3 fatty acid consumption can lower triglycerides by 25–30%, raise HDL cholesterol (HDL-C) by 1–3% and raise LDL-C by 5–10% if saturated fat intake remains constant.^[33] 2–4 g of eicosapentenoic acid and docosahexenoic acid per day are needed to achieve this triglyceride-lowering effect. Fish

oils have also been used in combination with other lipid-lowering agents. In patients with combined hyperlipidemia, the addition of 7.2 g/day of marine oils with simvastatin 10 mg/day brought about a better reduction in triglycerides than with the statin alone.^[34] There was no attenuation of the LDL-lowering effect of the statin with the addition of the fish oils. Patients with a sustained hypertriglyceridemia despite adequate treatment of LDL-C with a statin drug achieved a 20–30% reduction in triglycerides over a year of treatment with a concentrated fish oil supplement.^[35] Although having no LDL-C-lowering effect, fish oil supplements can be a useful adjunct in individuals with a mixed hyperlipidemia and persistently elevated triglyceride levels.

Garlic

Garlic has been advocated as an agent to lower blood pressure and cholesterol. Garlic contains sulfur-rich derivatives of the amino acid cysteine, including allicin, that are thought to give medicinal benefits. Little or no allicin is present in the intact garlic clove. When garlic is cut or crushed the enzyme allinase interacts with the cysteine compound alliin producing allicin. Allicin gives garlic its typical aroma and taste, but is fairly volatile and usually breaks down in a few hours at room temperature or after 20 min of cooking. Studies in isolated hepatocytes indicate that key enzymes in cholesterol biosynthesis, including HMG-CoA reductase, may be inhibited by the sulfur-containing compounds in garlic.^[36] A meta-analysis of five selected trials including a total of 410 individuals indicated a 9% reduction in cholesterol levels in the garlic-treated subjects.^[37] Since the publication of the meta-analysis, however, further studies have reported conflicting results. The discrepant results among studies may be explained by manufacturing differences among the garlic preparations. Deodorized garlic powder may not contain the active components thought to inhibit cholesterol synthesis. Fresh garlic may achieve a significant amount of allicin in the diet, but the odor and stomach upset caused by raw garlic make it a difficult agent to use for a cholesterol-lowering agent. Cooked garlic may be better tolerated but prolonged cooking will inactivate the sulfur-containing compounds thought to be beneficial. Garlic as part of a therapeutic lifestyle diet may be an adjunct for cholesterol lowering with standard therapy, but definitive studies have not been carried out.

Mediterranean Diet

The Mediterranean diet contains an abundance of fruits and vegetables, potentially helpful fats such as olive oil and fish oils, rare red meat and wine in low or moderate amounts. Individuals on a Mediterranean diet may lose more weight compared with other dietary approaches and have lower

total cholesterol and triglyceride levels, and higher HDL levels.^[38] In addition, multiple studies using a Mediterranean diet suggest that there may be a cardioprotective effect of these diets. The Dietary Approaches to Stop Hypertension and Therapeutic Lifestyle diets recommended by the NCEP are similar to a Mediterranean diet since both diets emphasize a high intake of fruits, vegetables and fiber, with a reduction in saturated fats (). These types of diets are recommended for anyone with cardiovascular disease or risk factors.

Table 1. Dietary Approaches to Stop Hypertension and Therapeutic Lifestyle diet components.

Diet component	DASH	TLC	Serving sizes
Grains	6–8 servings/day	7 servings/day	1 slice bread, 1 oz dry pasta or cereal
Vegetables	4–5 servings/day	5 servings/day	1 cup raw leafy vegetable, ½ cup vegetable
Fruits	4–5 servings/day	4 servings/day	1 medium fruit, ¼ cup canned fruit, ½ cup fruit
Fat-free or low-fat milk and milk products	2–3 servings/day	2–3 servings/day	1 cup milk, 1 cup yogurt
Lean meats, poultry and fish	<6 oz/day	<5 oz/day	
Nuts, seeds and legumes	4–5 servings/week	Counted in vegetable servings	⅓ cup (1½ oz), 2 tbsp seeds, ½ cup dry beans
Fats and oils	2–3 servings/day	Amount depends on daily calorie level	1 tsp soft margarine, 1 dressing, 1 tsp vegetable oil
Sweets and added sugars	5 or fewer servings/week	No recommendation	1 tbsp sugar, 1 tbsp jelly, 1 cup lemonade

DASH: Dietary Approaches to Stop Hypertension; tbsp: Tablespoon; tsp: Teaspoon; TLC: Therapeutic lifestyle. Data taken from [14,52].

Red Yeast Rice

Red yeast rice is a traditional Chinese medicinal agent prepared by culturing the yeast *Monascus purpureus* with rice. This process produces a group of compounds called monacolins. Monacolin K is lovastatin, the first commercially available statin on the market. Some of the other monacolins may have HMG-CoA reductase inhibitory effects also. In addition, some of the red yeast rice preparations contain phytosterols. The red yeast rice preparations that are available may contain different amounts of monacolin

K ranging from nearly undetectable levels to the equivalent of approximately 10 mg of lovastatin. A recent survey of 12 commercially available products indicated that the mean dose of lovastatin was approximately 6 mg/day.^[39] A randomized controlled trial using one particular formulation of red yeast rice for 12 weeks achieved a 22% reduction in LDL-C.^[40]

Red yeast rice has been used as an alternative to statins in statin-intolerant patients. A small survey of 25 patients unable to tolerate statins due to myalgias, gastrointestinal symptoms and liver enzyme abnormalities showed that red yeast rice was well tolerated, and that 92% were able to remain on therapy.^[41] The mean reduction in LDL-C in patients unable to tolerate statins was 19%. A randomized trial of 62 patients who discontinued statins due to myalgias compared red yeast rice with placebo over a 24-week period.^[42] There was a 21% reduction in LDL-C at 24 weeks. There was no difference in pain severity scores between the placebo or red yeast rice groups. Red yeast rice was compared with pravastatin in 43 patients with a history of statin discontinuation because of myalgias.^[43] LDL-C decreased by 30% in the red yeast rice group and 27% in the pravastatin group. Withdrawal from medication due to myalgias occurred in 5% (one patient) of the red yeast rice group and 9% (two patients) in the pravastatin group after 12 weeks. Although red yeast rice has a natural statin as its main lipid-lowering agent, it seems to be tolerated, probably because only low doses of the statin are present. The lipid-lowering effect may be enhanced by phytosterols that are present in many of the products. Because red yeast rice does contain a statin, however, there have been reports of myalgias and one case of rhabdomyolysis attributed to red yeast rice.^[42]

There are major concerns about red yeast rice as a long-term medicinal agent. Red yeast rice is considered a food or dietary supplement, but because it contains lovastatin, the US FDA has taken action against several of the products. Some of these products have been reformulated and no longer contain appreciable amounts of lovastatin. In addition, if the red yeast rice is not fermented correctly, the contaminant citrinin can be present. Citrinin is potentially nephrotoxic and may be cancer causing. In a recent survey of 12 commercially available red yeast rice products, one-third contained the potentially toxic citrinin.^[39] Because of the lack of standardization and concern about the presence of mycotoxins, caution will need to be used when considering the use of these products.

Intestinal Agents

The bile acid sequestrants (resins) bind bile acids in the GI tract preventing

the return of bile acids to the liver through the enterohepatic circulation. To produce more bile acids, the liver increases synthesis of cholesterol and upregulates LDL receptors, increasing the clearance of LDL-C from the circulation. The resins can reduce LDL-C by 10–20% when used as monotherapy. These agents are especially useful as adjunct agents to low doses of statins in individuals that cannot tolerate higher doses of these agents. An additional 20–25% reduction in LDL-C can be achieved with the addition of a resin to a statin. Colesevelam has also been shown to improve glycemic control in patients with Type 2 diabetes mellitus with a mean reduction in hemoglobin A_{1c} between 0.5 and 1% compared with placebo.^[44]

Ezetimibe is a selective cholesterol absorption inhibitor that prevents the absorption of dietary and biliary cholesterol through the intestinal wall. The selectivity of ezetimibe does not affect absorption of triglycerides, bile acids or fat soluble vitamins. The target of ezetimibe is the NPC1L1 protein.^[45] The binding of ezetimibe to this receptor blocks cholesterol uptake in the brush border membrane of the enterocyte. Following absorption, ezetimibe is glucuronidated in the intestinal wall and undergoes enterohepatic recirculation. The drug is then returned to its primary site of action in the intestine, limiting systemic exposure. Ezetimibe lowers LDL-C by between 15 and 20% as monotherapy, but may be more useful as adjunct therapy to lower-dose statins in a similar way to the resins. Outcome studies to determine if combination therapy with statins will achieve further cardiovascular risk reduction are ongoing.

Niacin

Niacin in high doses can lower total cholesterol and LDL-C, and has the greatest potential for raising HDL cholesterol. An early lipid-lowering study with immediate-release niacin showed a cardiovascular benefit. The Coronary Drug Project conducted between 1966 and 1975 evaluated the long-term efficacy of 3 g of niacin daily in a group of men who had a previous myocardial infarction.^[46] After 6 years the patients taking niacin had a lower incidence of nonfatal myocardial infarction. After 15 years of follow-up, the patients assigned to niacin had an 11% lower mortality than the placebo group, even though these subjects had stopped taking niacin 9 years earlier.^[47]

Studies combining niacin with a statin, however, have not been able to show additional risk reduction. The AIM-HIGH trial evaluated whether the addition of extended-release niacin added to statin therapy titrated to reduce the LDL-C to <70 mg/dl could bring about a further cardiovascular risk reduction.^[48] The study was stopped early because no additional

benefit was observed. Of note, the niacin therapy in this study was added to raise HDL cholesterol since the LDL-C was already treated to very low levels. The addition of niacin to a statin may be useful to further lower LDL-C in individuals that cannot tolerate high-dose statins because of side effects or cannot achieve the desired LDL-C goal with a statin alone.

Fibrates

The fibrates are a class of medications that are agonists of PPAR- α . The PPARs are nuclear transcription factors that modulate gene expression with effects on lipid and glucose metabolism. PPAR- α agonists lower triglyceride levels and mildly raise HDL-C with minimal change or a slight increase in LDL-C levels. This increase in LDL-C may be due to an increase in particle size and, thus, the cholesterol content of the LDL particles, and not an absolute increase in the number of LDL particles. Fibrates are mainly used as triglyceride-lowering agents and may be useful in individuals with mixed hyperlipidemia.

Gemfibrozil has been studied in both primary and secondary prevention trials. The VA-HIT compared 1200 mg of gemfibrozil with placebo in over 2500 men with coronary heart disease and low HDL-C levels.^[49] Gemfibrozil caused an increase in HDL-C levels by 6%, lowered triglycerides by 31% and caused no change in LDL-C. There was a 24% reduction in the combined end point of death from coronary disease, nonfatal myocardial infarction and stroke. Patients with metabolic syndrome or diabetes (high triglycerides and low HDL-C) seemed to derive the most benefit from therapy with gemfibrozil.^[50] This study suggests that patients with a mixed hyperlipidemia who cannot tolerate statins may obtain cardiovascular risk reduction using fibrates.

It is less clear if combining a fibrate with a statin can give further risk reduction. The ACCORD study compared the combination of simvastatin plus fenofibrate with simvastatin alone and failed to show any further cardiovascular risk reduction with combination therapy.^[51]

Conclusion

The NCEP recommends that LDL-C is the primary target of therapy to achieve cardiovascular risk reduction in both primary and secondary prevention patients. Statins have become medications of first choice because of their efficacy in lowering LDL-C, as well as numerous outcome studies proving a cardiovascular risk reduction. As many as 10% of individuals, however, may not be able to tolerate statins. Alternative approaches need to be designed for these patients. A combination of a

therapeutic lifestyle diet with careful use of supplements, such as plant stanols and sterols, as well as alternative lipid-lowering agents, can help patients achieve their LDL-C goals, and reduce cardiovascular risk.

The NCEP has emphasized a healthy lifestyle with a therapeutic lifestyle diet as the basis for cardiovascular risk reduction. In the future, greater emphasis will probably be placed on exercise and diet as a very effective way to modify cardiovascular risk as primary therapy and as adjunctive therapy to any pharmacological agents that are used. Risk reductions with a lifestyle program have the potential to mimic benefits seen with pharmacological therapy. An optimal lifestyle program can also help to avoid potential toxicity from medications. Further research to elucidate the benefits of a lifestyle program and how to easily implement these programs for our patients is needed.

Sidebar

Executive Summary

- The major adverse effects of statins are the potential for liver and muscle toxicity.
- The incidence of myalgias is reported to be approximately 5% in randomized clinical studies, but surveys of longer-term use suggest that myalgias may be experienced by >10% of patients.
- Alternative statin dosing schedules using once-, twice- or three-times a week, or every-other-day dosing, have been investigated as methods to reduce myalgias and achieve efficacy in lowering LDL cholesterol (LDL-C).
- Dietary therapy can be useful as adjunctive therapy to medication:
 - Replacing animal protein with soy protein can reduce total cholesterol and LDL-C;
 - 2 g/day of plant stanols and sterols in the diet reduces LDL-C by approximately 10%;
 - Ingestion of 2–10 g/day of soluble fiber in the diet can reduce LDL-C by approximately 7%;
 - The addition of fish oils to the diet for the prevention of cardiovascular events has been supported by a number of

clinical trials;

- Individuals on a Mediterranean diet lose more weight compared with other dietary approaches and have lower total cholesterol and triglyceride levels, and higher HDL levels.
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- Red yeast rice has been used as an alternative to statins in statin-intolerant patients.
- The bile acid sequestrants can reduce LDL-C by 10–20% when used as monotherapy.
- The addition of niacin to a statin may be useful in further LDL-C lowering in individuals that cannot tolerate high-dose statins because of side effects or cannot achieve the desired LDL-C goal with a statin alone.

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