

# Lipid Management in Adults

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**Goal:** The goal of this lesson is to discuss medical management of lipids in adult patients.

**Objectives:** At the conclusion of this knowledge based activity, successful participants should be able to:

- Describe dyslipidemia, including risk and contributing factors;
- List routine targets for therapy of a patient with dyslipidemia;
- Identify the primary steps of therapy for dyslipidemia; and
- Specify the uses and limitations of medications commonly used for treating dyslipidemia.

The past thirty to forty years have revealed a greater understanding of the risks related to cardiovascular disease in the U.S. The risk from high circulating levels of lipids, termed dyslipidemia, is now directly linked to coronary and vascular disease as a primary predictor of risk and occurrence of premature coronary heart disease. This article will briefly review the treatment of lipid disorders primarily based on the Adult Treatment Panel III (ATP III) recommendations.

Several major risk factors have been identified, and some can be reduced through lifestyle changes. However, other risks for dyslipidemia continue to be uncovered and further research is being conducted; notably, the Jupiter study identified the positive impact of statin-induced c-reactive protein reduction in patients with low LDL cholesterol to reduce incidence of cardiovascular events. Modifiable risk factors include obesity (BMI > 30), physical inactivity, cigarette smoking, and a meal plan that can readily produce atherogenesis. Researchers continue to uncover genetic and physiologic links to dyslipidemia, including proinflammatory factors, prothrombotic factors, homocysteine, lipoprotein, and the role of impaired fasting glucose. Major independent risk factors for coronary heart disease (CHD) include cigarette smoking, hypertension, low HDL-cholesterol, a family history of premature

coronary heart disease (CHD), and advancing age (men >45 years, women >55 years). Diabetes mellitus is now recognized as a coronary risk equivalent.

The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III (ATP III)] recommend targeting the LDL-cholesterol (LDL-C) first. The purpose of targeting LDL-C first is to reduce the number of small dense particles. Primary prevention techniques to achieve this goal would include reduction of saturated fat and cholesterol in a patient's meal plan and weight control when indicated. Increased physical activity generates positive effects for lipid control also. The secondary lipid target should focus on raising HDL-C and lowering triglycerides (TG). Generally, the goals of treatment are for long-term prevention and short-term prevention of cardiovascular events. Should a patient have coronary heart disease or CHD risk equivalents, the LDL-C goal is <100 mg/dL. An optional LDL goal < 70 mg/dl is reasonable in very high risk patients. Other risk equivalents recognized in the ATP III plan, in addition to diabetes, include clinical forms of atherosclerotic disease and multiple risk factors that indicate a 10-year risk for coronary heart disease of >20%. A patient with two or more risk factors has an

LDL-C goal of <130 mg/dL, while the patient with 0-1 risk factor has an LDL-C goal of < 160 mg/dL. NCEP recommendations suggest the goal for total cholesterol is < 200 mg/dL, with 200-239 mg/dL considered borderline and >240 mg/dL high. High density lipoproteins (HDL) cholesterol is considered low when less than 40 mg/dL and high when greater than 60 mg/dL.

Causes of secondary dyslipidemia include diabetes mellitus, hypothyroidism, chronic renal failure, obstructive liver disease, and drugs that elevate LDL cholesterol and lower HDL cholesterol (progestins, corticosteroids, isotretinoin, anabolic steroids). Preventive measures to lower LDL cholesterol result in decreased total and coronary mortality, major coronary events, and stroke. The first step in treatment is to implement therapeutic lifestyle changes. These changes include dietary recommendations that reduce the intake of cholesterol raising nutrients (<7% of total daily calories as saturated fats, dietary cholesterol of <200 mg daily), ingestion of plant stanols/sterols (2 Gm/day) and soluble fiber (10-25 Gm/day), weight reduction, and increased physical activity. Alcohol consumption should be limited with dyslipidemic patients also.

### **Medications for Dyslipidemia**

Six categories of therapeutic medications are used in the treatment of dyslipidemia including: HMG-CoA reductase inhibitors (statins), selective intestinal cholesterol absorption inhibitors, fibric acid derivatives (fibrates), bile acid sequestrants, niacin/nicotinic acid, and omega-3 fatty acids.

HMG-CoA reductase inhibitors, commonly referred to as statins, are the most widely used lipid-lowering agent and often the first choice agent, with their primary lipoprotein effect of lowering LDL-C and their secondary benefits of decreased TG and increased HDL-C. As an additional benefit, statins may increase the buoyancy or particle size of LDL-C. Statins reduce LDL-C by competitively inhibiting HMG-CoA reductase, resulting in lowered endogenous cholesterol. Statins are commonly administered once daily in the evening to allow for maximum effect, because daily peak cholesterol synthesis occurs at night. General recommendations suggest a starting dose at a low level and gradual increases in dose to achieve the maximum desired effect, with adjustments no more often than every 6 weeks.

Statins are well tolerated, but some side effects have been reported. They should be prescribed cautiously in those with impaired renal function. The more common adverse reactions include headache, nonspecific muscle and joint pain, and gastrointestinal complaints, such as nausea, diarrhea, constipation, flatulence, or abdominal pain.

Significant elevations of liver enzymes can occur. There have been reports of hepatic toxicity associated with statins: from 0.1% to 0.4% in patients on usual daily doses and up to 2% in patients on maximum dosage. Myopathy, a disease of the muscle, and rhabdomyolysis, the breakdown of striated muscle, have been reported in 1% to 5% of patients and in 1 in 2000 patients, respectively. Therefore, patients should be instructed to report any muscle weakness, tenderness, pain, or fever. Laboratory testing of serum creatinine kinase can confirm or rule out rhabdomyolysis. Rhabdomyolysis, a more severe adverse affect, typically presents with additional signs and symptoms that include weight gain from fluid retention, fever, nausea, tachycardia, and dark or colored urine.

Most statins are metabolized through the cytochrome P-450 3A4 pathway in the liver. Concurrent medications and foods (such as grapefruit juice) that are also metabolized through this system should be used cautiously and monitored for increased levels and risks of adverse reactions. A baseline lipid profile, CPK enzyme, liver function, and renal function tests should be conducted prior to initiating statin therapy. Monitoring lipid profiles and liver function tests should be done every 12 weeks in the first 6 months of treatment and periodically thereafter.

The primary lipoprotein affected by bile acid sequestrants is LDL-C, with a secondary effect of a modest increase in HDL-C. They can often increase TG, limiting their broad use. According to the ATP-III guidelines, bile acid sequestrants should only be used as monotherapy in cases with TG < 200. Bile acid sequestrants bind to bile acids through the exchange of chloride ions in the intestinal lumen, resulting in decreased cholesterol production. They also inhibit enterohepatic circulation of bile acids and increase elimination of fecal acidic steroids.

Bile acid sequestrants are available as a tablet and as a powder for dilution. Dosing can be once or twice daily. Lower doses are recommended for initial therapy and can be titrated up every 4 to 8 weeks as necessary to reach optimal or maximum dose.

Colesevelam is listed as category B, indicating no evidence of risk in humans, whereas cholestyramine and colestipol are listed as category C. Bile acid sequestrants are contraindicated when the TG level is > 400 mg/dL and in primary biliary cirrhosis. As noted above, they should only be used as monotherapy when the TG level is less than 200 mg/dL. Patients with renal insufficiency, volume depletion, and chronic constipation are not good candidates for bile acid sequestrants.

Adverse effects with bile acid sequestrants are mostly gastrointestinal in nature, due to the lack of systemic absorption. The most common complaints are headache, unpalatable taste, nausea, bloating, flatulence, and constipation. Bile acid sequestrants can bind to other medications, resulting in decreased absorption and clinically significant drug interactions. Therefore, it is recommended to separate bile acid sequestrants from other medications by administering them 1 hour before or 4 hours after the bile acid sequestrants, although some evidence suggests colesevelam does not appear to have these drug interactions. Baseline lipid profiles with a follow-up at 4 to 6 weeks for efficacy are recommended for bile acid sequestrants. Prolonged use of bile acid sequestrants may also cause hyperchloremic acidosis. A patient compliance assessment should be conducted due to the bile acid sequestrant-associated gastrointestinal discomfort.

The cholesterol absorption inhibitor's (ezetimibe, Zetia) primary action is to reduce LDL-C. Studies suggest that ezetimibe may also slightly decrease TG and increase HDL-C. Cholesterol absorption inhibitors have been used with statins for their effect on LDL-C, but new studies suggest niacin added to statin therapy may produce better clinical outcomes. Cholesterol absorption inhibitors reduce cholesterol by selective inhibition of the absorption of cholesterol from the small intestine. This results in a decreased delivery of cholesterol to the liver and a reduction of hepatic cholesterol stores, with an overall lowering of cholesterol, primarily LDL-C. Initial and maintenance dosage is 10 mg once daily and may be used in conjunction with statins or bile acid sequestrants, although ezetimibe dose should be taken either 2 hours before or 4 hours after bile acid sequestrant. Ezetimibe is listed as category C for pregnancy and should be avoided to reduce risks. Caution should be used in patients with hepatic dysfunction. Ezetimibe (Zetia) is generally well tolerated with minimal adverse effects. The most common complaints are gastrointestinal, such as diarrhea and abdominal pain, as well as back pain,

arthralgia, and sinusitis. Baseline lipid profiles and liver function tests should be conducted prior to initiating therapy. When used concurrently with statins, liver enzymes should be monitored prior to initiating statin therapy and every 12 weeks in the first 6 months of treatment and periodically thereafter.

Fibrates (fenofibrate/Tricor, Gemfibrozil/Lopid) exert their lipoprotein-lowering effects on TG, with additional benefits of increasing HDL-C. These agents are more commonly prescribed when elevations in TG are present. They are also useful in combination with statins to cover the entire spectrum of lipoprotein abnormalities in diabetic dyslipidemia. However, close monitoring is warranted with combination therapy. Although the mechanism of action is not clear, these agents can increase lipoprotein lipase, resulting in the breakdown of very low density lipoprotein (VLDL). Fibrates are administered once to twice daily, often prior to or with a meal. The dosage is titrated to the lipid lowering needed to achieve target goals. However, initial therapy commonly starts with a lower dose and is then adjusted every 4 to 8 weeks as necessary. Fibrates are listed as category C for pregnancy and should be avoided to reduce risks. Lower dosages should be used for patients with renal dysfunction and the elderly. Preexisting gallbladder disease, hepatic dysfunction, and severe renal dysfunction are considered contraindications. Common adverse effects are gastrointestinal and include indigestion, nausea, flatulence, diarrhea, and abdominal pain. Rare side effects that have been reported are rash, fever, weight gain, muscle weakness, drowsiness, decreased potassium levels, anemia, and low white blood cell count. Although cases of myopathy and rhabdomyolysis have been seen in monotherapy, this is more commonly seen in conjunction with HMG-CoA reductase inhibitors. Fibrates are highly protein bound and can increase the adverse reactions of medications that are also highly protein bound. Common protein-bound medications include warfarin and sulfonyleureas.

TG and cholesterol levels should be measured prior to initiating fibrate therapy and at 3- to 6-month intervals. Liver function tests and complete blood cell counts should also be monitored at baseline and 6-month intervals. If liver enzymes are greater than 3 times the upper limit of normal, stop therapy. Hematologic changes, including decreased hemoglobin, hematocrit, thrombocytopenia, and neutropenia, can occur. The primary lipoprotein effect of niacin is an increase in HDL-C, with a

modest reduction in TG and LDL-C. Although niacin can be useful in increasing HDL-C levels, it can also increase blood glucose levels, especially in prediabetes or newly diagnosed patients.

Niacin or nicotinic acid reduces the breakdown of HDL and selectively decreases the excretion of HDL apo-A-1, which stimulates reverse cholesterol transport in hepatic cells. Additionally, niacin reduces hepatic VLDL production, resulting in a reduction in LDL-C and TG levels. Niacin is available in an immediate-release, sustained-release, and extended-release dose; these formulations should not be interchanged. Immediate-release nicotinic acid may be preferred over sustained release for initial treatment, due to unfavorable adverse drug effects with the sustained release formulation. This preference is true when therapy starts with small doses as necessary and tolerated. Doses may start as low as 100 mg 3 times daily and gradually increased to the maximum dose of 3 g per day in divided doses. Sustained-release nicotinic acid can be initiated at 250 mg twice daily and titrated up as tolerated to a maximum dose of 2 g per day, administered in a single or divided dose. Niacin is listed as category C for pregnancy and should be avoided to reduce risks. Patients with preexisting gout, heavy alcohol use, or renal dysfunction are not good candidates for this therapy, so close monitoring is needed if used. Liver dysfunction, active peptic ulcer disease, and arterial bleeding are contraindications.

The adverse effects of niacin can limit use. The more common effects include headache, hypotension, gastrointestinal discomfort, such as nausea, vomiting, and diarrhea, and the dermatological reactions of flushing, pruritis, and rash. Flushing typically decreases with continuous use and can be reduced by taking niacin with meals. Aspirin taken once daily, 30 minutes prior to the niacin dose, can also minimize flushing. Patients on large doses of niacin, greater than 2 g per day, may be at increased risk of hepatotoxic effects. Significant elevations of liver enzymes can occur. Discontinue treatment when liver enzymes are greater than 3 times the upper limit of normal. Niacin is known to inhibit the release of insulin from the beta cell, resulting in hyperglycemia. Alcohol and hot drinks have been reported to increase flushing and pruritis effects. A baseline lipid profile, liver function, uric acid, and blood glucose levels should be performed prior to initiating niacin therapy and repeated at 6-week intervals while adjusting the dosage. Lipid profiles should be reviewed at 3- to 6-month intervals.

Use of omega-3 fatty acids (or Lovaza) primarily lowers Triglyceride levels and increases HDL-C levels as a secondary effect. The HDL effect is generally seen only when higher doses are used. LDL-C levels tend to increase. Omega-3 fatty acids lower elevated TG through a reduction in hepatic VLDL production. Omega-3 fatty acids reduce the quantity of free fatty acids available for TG synthesis, lowering VLDL synthesis and increasing lipoprotein lipase activity, which results in TG clearance. The initial dose of omega-3 fatty acids is 1 to 2 1000-mg capsules daily to a maximum dosage of 4 g per day. It should be taken with food to minimize gastrointestinal adverse effects. There are no adequate studies with pregnant women; therefore, omega-3 fatty acids should be avoided during pregnancy. Close monitoring and assessment should be used in patients with renal or hepatic dysfunction and those at high risk of hemorrhage. The more common adverse effects are dizziness and gastrointestinal discomfort, such as dyspepsia, nausea, and abdominal pain. Rare adverse effects of headache, pruritis, and hyperglycemia have been reported. Omega-3 fatty acids may decrease the production of thromboxane A-2, resulting in an increase in bleeding time, and INR can increase in concurrent use with warfarin. A baseline lipid profile and liver function tests should be performed prior to starting omega-3 fatty acids therapy and repeated at regular intervals, especially while adjusting dosage.

## Summary

Patients require a significant amount of education regarding their dyslipidemia therapy. Perhaps the most significant challenge is helping patients make the critical behavioral changes needed to improve their dyslipidemia non-pharmacologically, especially modification of their diet and physical activity. This step in care mandates several repeat sessions to review the plan and methods that can be employed to assist the patient and caregiver(s) in achieving positive steps in controlling their abnormal lipid levels. It seems that the patient often does not grasp the facts or impact that positive steps in these areas can provide for the patient's benefit. It can be helpful to develop a program that utilizes the Framingham Risk Assessment to effectively communicate to the patient the importance of a 7-10% decrease in body weight and effective control of lipids and blood pressure. This can create some discrepancy that the patient sees between their current status and what the change could mean. The Framingham risk assessment is available at this website:

[http://hp2010.nhlbi.nih.net/atpIII/calculator.asp?user\\_type=prof](http://hp2010.nhlbi.nih.net/atpIII/calculator.asp?user_type=prof).

The medication plan for the patient should be kept as simple as possible, with good counseling techniques used for patient instruction. The patient and caregivers should feel free to ask all questions about the therapy and what to expect with the medication. If any of the medications should be stopped for any reason, those reasons should be noted. The timing and type of ongoing laboratory or other monitoring should be reviewed with the patient also.

important steps in treating lipids in patients with diabetes. Triglycerides, HDL cholesterol and particle size of the LDL cholesterol must be addressed in the treatment plan. Achieving optimal levels of these lipoproteins should be considered when choosing drug therapy with a combination of more than one agent necessary for achieving the goal. Continued vigilance and consistent follow-up with the patient is needed for aiding in success. If a patient can envision their capability for developing control, then the potential for long-term success of therapy is improved.

The primary lipid target for patients with diabetes is the LDL cholesterol. Therapeutic lifestyle changes, including proper application of meal planning, physical activity, and daily health habits, are

| Drug Class, Agents and Daily Doses     | Lipid/Lipoprotein Effects                                                                     | Side Effects                                                                                | Contraindications                                                                                                             | Clinical Trial Results                                                                               |
|----------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| HMG CoA reductase inhibitors (statins) | LDL ↓18-55%<br>HDL ↑5-15%<br>TG ↓7-30%                                                        | Myopathy<br>Increased liver enzymes                                                         | Absolute:<br>• Active or chronic liver disease<br>Relative:<br>• Concomitant use of certain drugs                             | Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality |
| Bile acid Sequestrants                 | LDL ↓15-30 %<br>HDL ↑3-5%<br>TG No Change or Increase                                         | Gastrointestinal distress<br>Constipation<br>Decreased absorption of other drugs            | Absolute:<br>• dysbeta-lipoproteinemia<br>• TG >400 mg/dl<br>Relative:<br>• TG >200 mg/dl                                     | Reduced major coronary events and CHD deaths                                                         |
| Nicotinic acid                         | LDL ↓5-25%<br>HDL ↑15-35%<br>TG ↓20-50%                                                       | Flushing<br>Hyperglycemia<br>Hyperuricemia (or gout)<br>Upper GI distress<br>Hepatotoxicity | Absolute:<br>• Chronic liver disease<br>• Severe gout<br>Relative:<br>• Diabetes<br>• Hyperuricemia<br>• Peptic ulcer disease | Reduced major coronary events, and possibly total mortality                                          |
| Fibric acids                           | LDL ↓5-20%<br><i>(may be increased in patients with high TG)</i><br>HDL ↑10-20%<br>TG ↓20-50% | Dyspepsia<br>Gallstones<br>Myopathy<br>Unexplained non-CHD deaths in WHO study              | Absolute:<br>• Severe renal disease<br>• Severe hepatic disease                                                               | Reduced major coronary events                                                                        |