

Current Guidelines and Treatments for Hyperlipidemia

This post aims to provide an in-depth understanding of hyperlipidemia, its current guidelines, and treatments. Hyperlipidemia, characterized by elevated levels of lipids in the blood, is a significant risk factor for cardiovascular diseases (CVD), which remain the leading cause of mortality worldwide.

Understanding Hyperlipidemia

Hyperlipidemia encompasses various lipid abnormalities, including elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and reduced high-density lipoprotein cholesterol (HDL-C).

Key Lipid Parameters

- Total Cholesterol: Ideal levels are less than 200 mg/dL.
- LDL: Often termed “bad cholesterol,” optimal levels in healthy adults are less than 100 mg/dL.
- HDL: Known as “good cholesterol,” levels above 60 mg/dL are considered protective.
- Triglycerides: Normal levels are less than 150 mg/dL.

Guidelines for Managing Hyperlipidemia

The management of hyperlipidemia primarily focuses on reducing the risk of atherosclerotic cardiovascular disease (ASCVD). ASCVD includes coronary artery disease, cerebrovascular disease and peripheral artery disease. The American College of Cardiology (ACC) and the American Heart Association (AHA) provide comprehensive guidelines.

In patients with known ASCVD, the LDL goal is under 55-70 mg/dL depending on risks. Those with diabetes and ASCVD have a goal of under 55 mg/dL, while diabetics without known ASCVD have a goal of less than 70 mg/dL. The LDL goal for those with chronic kidney disease stage 3 or higher is less than 70 mg/dL.

Key Recommendations

1. Lifestyle Modifications:

- Diet: Adopting a heart-healthy diet, such as the Mediterranean or DASH diet, which emphasizes fruits, vegetables, whole grains, lean proteins, and healthy fats.
- Exercise: Engaging in at least 150 minutes of moderate-intensity aerobic exercise per week.
- Weight Management: Achieving and maintaining a healthy weight.
- Smoking Cessation: Eliminating tobacco use to improve lipid profiles and overall cardiovascular health.

2. Pharmacotherapy:

- Statins:

- Mechanism of Action: Statins inhibit HMG-CoA reductase, the enzyme responsible for the synthesis of cholesterol in the liver. This leads to upregulation of LDL receptors, increasing the clearance of LDL from the bloodstream.
- Lipid Reduction: Statins can lower LDL levels by 20-60%, depending on the specific statin and dose. Approximate reductions are 54% with maximum dose atorvastatin, 63% with maximum dose rosuvastatin. Less potent statins provide lower reductions.

- Cardiovascular Benefits: Statins significantly reduce the risk of major cardiovascular events (heart attack, stroke, and death from cardiovascular causes) by 20-30%. They also reduce the progression of atherosclerosis and stabilize existing plaques, lowering the risk of plaque rupture and subsequent cardiovascular events.

- FDA Indications: Statins are approved for the treatment of primary hyperlipidemia (elevated LDL), mixed dyslipidemia (high LDL and low HDL), familial hypercholesterolemia (hereditary high LDL), and prevention of cardiovascular events in individuals with or at high risk for ASCVD.

- Use: Statins are the cornerstone of lipid-lowering therapy, particularly for individuals with clinical ASCVD, LDL levels ≥ 190 mg/dL, diabetes aged 40-75 with LDL 70-189 mg/dL, and those with an estimated 10-year ASCVD risk of 7.5% or higher. High intensity statins (atorvastatin or rosuvastatin) are recommended for those with known ASCVD.

- Ezetimibe:

- Mechanism of Action: Ezetimibe (Zetia) inhibits the Niemann-Pick C1-Like 1 (NPC1L1) protein on the intestinal brush border, reducing the absorption of cholesterol from the diet.

- Lipid Reduction: Ezetimibe can lower LDL levels by approximately 15-20% by itself or when added to a statin. Some patients are super responders with close to 40% reductions in LDL.

- Cardiovascular Benefits: Ezetimibe has been shown to reduce the risk of cardiovascular events, particularly when used in combination with statins, as evidenced by the IMPROVE-IT trial, which demonstrated a reduction in major cardiovascular events in patients with recent acute coronary syndrome.

- FDA Indications: Ezetimibe is approved for the treatment of primary hyperlipidemia and homozygous familial hypercholesterolemia, alone or in combination with a statin.

- Use: Ezetimibe is used in addition to statins when LDL-C goals are not met or for patients who are statin-intolerant.

- PCSK9 Inhibitors:

- Mechanism of Action: PCSK9 inhibitors, such as evolocumab (Repatha) are monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 binds to LDL receptors and promotes their degradation; blocking PCSK9 increases the number of LDL receptors available to clear LDL from the blood.

- Lipid Reduction: PCSK9 inhibitors can reduce LDL levels by 43-64%.

- Cardiovascular Benefits: Evolocumab has been shown to significantly reduce the risk of cardiovascular events, including heart attack, stroke, and death from cardiovascular causes. The FOURIER trial demonstrated these benefits in high-risk patients.

- FDA Indications: Evolocumab is approved in adults with established cardiovascular disease (CVD) to reduce the risk of myocardial infarction, stroke, and coronary revascularization (stent or CABG). They are also approved to reduce LDL, alone or in combination with other LDL lowering therapies, in adults with primary hyperlipidemia and heterozygous familial hypercholesterolemia (HeFH). It is approved in addition to other LDL lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH).

- Use: Most often used for high-risk patients, particularly those with familial hypercholesterolemia or those who have not achieved target LDL levels with maximum tolerated statin and ezetimibe therapy, or for those intolerant to other therapies.

- Antilipemic Small Interfering Ribonucleic Acid (siRNA) Agents

- Mechanism of action: Inclisiran (Leqvio) interferes with and breaks down PCSK9. This increases LDL receptors, which increase LDL uptake and lowers LDL levels in the circulation.

- Lipid Reduction: 50% LDL reduction when added to diet and maximally tolerated statin.
- Cardiovascular Benefits: Data is lacking on cardiovascular benefits.
- FDA Indications: Indicated, in addition to diet and statin, for the treatment of primary hyperlipidemia and heterozygous familial hyperlipidemia to reduce LDL.
- Use: Most often used for patients who are not at LDL goal with a statin plus ezetimibe, or who cannot tolerate PCSK9 inhibitors.

- Bempedoic Acid:

- Mechanism of Action: Bempedoic acid (Nexletol) inhibits ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase in the cholesterol synthesis pathway, reducing cholesterol synthesis in the liver and increasing LDL receptors to remove LDL from the blood.
- Lipid Reduction: Bempedoic acid can lower LDL levels by 15-25%.
- Cardiovascular Benefits: Bempedoic acid has been shown to reduce the risk of cardiovascular death, non-fatal heart attack, non-fatal stroke, as well as heart attack and coronary revascularization (stent or CABG).
- FDA Indications: Bempedoic acid is approved for the treatment of primary hyperlipidemia (including heterozygous familial hypercholesterolemia) as an additional agent in patients who do not meet cholesterol treatment goals with dietary modification plus maximally tolerated lipid-lowering therapies (high-intensity statin plus ezetimibe and/or a PCSK9 monoclonal antibody). It is also indicated to reduce the risk of myocardial infarction and coronary revascularization in adults who are unable to take recommended statin therapy and have known cardiovascular disease (CVD) or are at high risk for a CVD.
- Use: Particularly useful for patients who are statin-intolerant or require additional LDL reduction in addition to statin therapy.

3. Pharmacotherapy for Hypertriglyceridemia (High Triglycerides):

- Statins: Statins can lower triglycerides by 22-45%.

- Fibrates:

- Mechanism of Action: Fibrates activate peroxisome proliferator-activated receptor-alpha (PPAR- α), leading to increased oxidation of fatty acids, reduced hepatic production of triglycerides, and increased lipoprotein lipase activity.
- Lipid Reduction: Fibrates can lower triglyceride levels by 30-50% and can also modestly increase HDL levels.
- Cardiovascular Benefits: Fibrates have shown benefits in reducing cardiovascular events in patients with high triglyceride levels, particularly those with diabetes and metabolic syndrome. However, their overall impact on reducing major cardiovascular events remains less definitive compared to statins. As such, treatment of high triglycerides is usually recommended for those with known or high risk for ASCVD or those with levels over 500.
- FDA Indications: Fibrates are approved for the treatment of severe hypertriglyceridemia (triglycerides ≥ 500 mg/dL) to reduce the risk of pancreatitis and for the treatment of mixed dyslipidemia.

- Omega-3 Fatty Acids (Fish Oil):

- Mechanism of Action: Omega-3 fatty acids (EPA and DHA) reduce hepatic production of triglycerides and increase triglyceride clearance by enhancing lipoprotein lipase activity.
- Lipid Reduction: Prescription omega-3 fatty acids can lower triglyceride levels by 20-50%. Over the counter fish oils and krill oil have consistently shown a lack of benefit and are no longer recommended for cardiovascular prevention.

- Cardiovascular Benefits: High-dose EPA (icosapent ethyl), the active ingredient in Vascepa, has been shown to reduce the risk of major cardiovascular events in patients with elevated triglycerides and high cardiovascular risk, as demonstrated by the REDUCE-IT trial.
- FDA Indications: Prescription omega-3 fatty acids are approved for the treatment of severe hypertriglyceridemia (triglycerides ≥ 500 mg/dL), for triglycerides over 150 mg/dL with known ASCVD, or with diabetes and 2 or more risk factors for ASCVD.
- Niacin:
 - Mechanism of Action: Niacin inhibits hepatic synthesis of triglycerides and very low-density lipoprotein (VLDL), leading to reduced LDL and triglyceride levels and increased HDL levels.
 - Lipid Reduction: Niacin can lower triglycerides by 20-50%, lower LDL by 5-25%, and increase HDL by 15-35%.
 - Cardiovascular Benefits: While niacin effectively improves lipid profiles, its impact on reducing cardiovascular events is less clear, and its use is often limited by side effects such as flushing and hepatotoxicity.
 - FDA Indications: Niacin is approved for the treatment of dyslipidemia to reduce elevated LDL, total cholesterol, triglycerides, and to increase HDL.

Monitoring and Follow-Up:

- Regular follow-up to monitor lipid levels and assess adherence to treatment and lifestyle modifications.
- Periodic reassessment of ASCVD risk and potential adjustment of therapy.

Emerging Therapies and Research

Ongoing research continues to expand the therapeutic landscape of hyperlipidemia. Novel agents, such as inclisiran, a small interfering RNA that targets PCSK9 synthesis, and bempedoic acid are showing promise. Additionally, studies on gene editing and other innovative approaches hold potential for future treatments.

Conclusion

Managing hyperlipidemia is a dynamic and multifaceted process. Adherence to current guidelines, lifestyle modifications, and pharmacotherapy remain the pillars of effective management. Guideline directed treatment, emerging therapies, and regular follow-up offer hope for decreasing the risks of ASCVD.