
APPROACH TO THE PATIENT WITH DYSLIPIDEMIA

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ABSTRACT

In evaluating a patient with dyslipidemia the initial step is to decide which particular lipid/lipoprotein abnormalities need to be evaluated and whether they need treatment. These disorders can be divided into elevations of LDL-C, triglycerides, non-HDL-C, and Lp(a) and decreases in plasma HDL-C. Frequently a patient can have multiple lipid/lipoprotein abnormalities. The next step is to rule out secondary causes that could account for the abnormal lipid/lipoprotein levels. These secondary causes can be due to diet, various disease states, or drug therapy. One should be suspicious of a secondary cause if a patient suddenly develops a lipid/lipoprotein abnormality or the lipid/lipoprotein profile suddenly worsens. Next one should consider the possibility of a genetic disorder and therefore ask whether relatives have either premature cardiovascular disease, lipid disorders, or are receiving lipid lowering medications. If the triglyceride levels are markedly elevated one should inquire about a family history of pancreatitis. When the lipid/lipoprotein abnormality is markedly abnormal or begins at a young age, the likelihood of a genetic disorder is increased and the family history assumes even greater importance. In most circumstances a routine lipid panel consisting of plasma triglycerides, total cholesterol, HDL-C, and calculated LDL-C and non-HDL-C provides sufficient information to appropriately decide on who to treat and the best treatment approach. However, it should be recognized that there are certain situations where more sophisticated and detailed laboratory studies

can be helpful. The purpose of treating lipid disorders is to prevent the development of other diseases, particularly cardiovascular disease. Thus, the decision to treat should be based on the risk of the hyperlipidemia leading to those medical problems. Several guidelines have been published that discuss in detail cardiovascular risk assessment and provide recommendations on treatment strategies. Additionally, calculators are available on-line to determine an individual patient's risk of developing cardiovascular disease in the next 10 years or their lifetime risk. In the prevention of cardiovascular disease, the main priority is to lower the LDL-C levels. Reductions in other apolipoprotein B containing lipoproteins may be instituted if LDL-C levels are at goal. Depending on the specific guideline the percent reduction in LDL-C and/or the goal LDL-C will vary depending upon the patient profile. When LDL-C levels are at goal but triglyceride and non-HDL-C levels are still elevated a recent study suggests further treatment with icosapent ethyl may be beneficial. Whether decreasing Lp(a) is beneficial in preventing cardiovascular disease is uncertain and further studies are in progress. Lifestyle changes are the initial treatment but in most patients' drug therapy will be necessary.

INTRODUCTION

The initial step is to decide which particular lipid/lipoprotein abnormalities need to be evaluated and whether they need treatment. These disorders

can be divided into elevations of LDL-C, triglycerides, non-HDL-C, and Lp(a), and decreases in HDL-C. An increase in non-HDL-C accompanies an increase in LDL-C and/or triglycerides levels. Often a patient can have multiple lipid/lipoprotein abnormalities. For example, it is not uncommon for a patient to have high triglycerides with low HDL-C levels or high LDL-C and high Lp(a) levels.

From a clinical point of view, one is not usually concerned if the LDL-C, Lp(a), or triglyceride levels are low or if the HDL-C level is high. Very low levels of LDL-C and/or triglycerides suggest the presence of other medical issues such as hyperthyroidism, malabsorption, liver disease, chronic infections, cancer, etc. On rare occasions very low LDL-C levels or triglyceride levels can be due to genetic disorders (1). Very high HDL-C levels can also be due to genetic causes (2).

RULE OUT SECONDARY CAUSES

The next step is to rule out secondary causes that could account for the abnormal lipid/lipoprotein levels. These secondary causes can be due to diet, various disease states, or medications. One should be suspicious of a secondary cause if a patient suddenly develops a lipid/lipoprotein abnormality or the lipid/lipoprotein profile suddenly worsens. Patients with genetic abnormalities causing dyslipidemia can have their disorder worsen if they develop secondary causes that further adversely affect lipid/lipoprotein levels.

The key is that if one corrects the secondary cause the lipid/lipoprotein abnormality can often markedly improve or even disappear. For example, hypothyroidism can be accompanied by striking increases in LDL-C levels and the treatment of hypothyroidism can result in a large decrease in LDL-C, often to normal levels (3). Likewise, an improvement in glycemic control in a patient with poorly controlled diabetes may result in a large decrease in serum triglyceride levels (4). Occasionally, the presence of dyslipidemia leads to the discovery of an unrecognized secondary disorder that requires treatment.

Similarly stopping certain drugs can greatly improve the lipid profile (5). For example, in some postmenopausal women with hypertriglyceridemia stopping oral estrogen therapy can result in a marked decrease in triglyceride levels (3). The disorders and drugs that cause lipid/lipoprotein abnormalities are shown in tables 1-7. It should be noted that many disorders and drugs can cause multiple lipid abnormalities. The effects of disorders and drugs in an individual patient can vary depending on genetic background and the presence of other disorders and drugs that effect lipid/lipoprotein levels. For an extensive discussion of the secondary disorders that alter lipid and lipoprotein metabolism please refer to the individual Endotext chapters on these disorders. For additional information on the effect of drugs on lipid and lipoprotein metabolism please see the Endotext chapter on this topic (5).

| Table 1. Disorders Associated with an Increase LDL in Cholesterol Levels |
|---|
| Increased intake of saturated or trans fatty acids |
| Hypothyroidism |
| Obstructive liver disease |
| Nephrotic syndrome |
| Pregnancy |
| Growth hormone deficiency |
| Anorexia nervosa |
| Monoclonal gammopathy |
| Cushing's syndrome |
| Acute intermittent porphyria |
| Hepatoma |

| Table 2. Drugs That Increase LDL Cholesterol Levels |
|--|
| Cyclosporine and tacrolimus |
| Amiodarone |
| Glucocorticoids |
| Danazol |
| Some progestins |
| Protease inhibitors |
| Anabolic steroids |
| Androgen deprivation therapy |
| Retinoids |
| Thiazide diuretics |
| Loop diuretics |
| Thiazolidinediones |
| SGLT2 inhibitors |

| Table 3. Disorders Associated with an Increase in Triglyceride Levels |
|--|
| Obesity |
| Alcohol intake |
| High simple carbohydrate diet |
| Diabetes |
| Metabolic syndrome |
| Polycystic ovary syndrome |
| Hypothyroidism |
| Chronic renal failure |
| Nephrotic syndrome |
| Pregnancy |
| Inflammatory diseases (Rheumatoid arthritis, Lupus, psoriasis, etc.) |
| Infections |
| Acute stress (myocardial infarctions, burns, etc.) |
| HIV |
| Cushing's syndrome |
| Growth hormone deficiency |
| Lipodystrophy |
| Glycogen Storage disease |
| Acute hepatitis |
| Monoclonal gammopathy |

| Table 4. Drugs That Increase Triglyceride Levels |
|---|
| Alcohol |
| Oral Estrogens |
| Tamoxifen/Raloxifene |
| Glucocorticoids |
| Retinoids |
| Beta blockers |
| Thiazide diuretics |
| Loop diuretics |
| Protease Inhibitors |
| Cyclosporine, sirolimus, and tacrolimus |
| Atypical anti-psychotics |
| Bile acid sequestrants |
| L-asparaginase |
| Androgen deprivation therapy |
| Cyclophosphamide |
| Alpha-interferon |
| Propofol |

| Table 5. Disorders Associated with a Decrease in HDL Cholesterol Levels |
|--|
| Marked Hypertriglyceridemia |
| Obesity |
| Metabolic syndrome |
| Low fat intake |
| Infection |
| Inflammation |
| Malignancy |
| Severe liver disease |
| Polycystic ovary syndrome |
| Paraproteinemia (artifact of some assays) |

| Table 6. Drugs That Decrease HDL Cholesterol Levels |
|--|
| Anabolic steroids |
| Danazol |
| TZD + fibrate (idiosyncratic reaction) |
| Beta-blockers |
| Progestins |
| Anti-psychotics |

| Table 7. Disorders or Drugs Associated with an Increase in Lp(a) Levels |
|--|
| Chronic Kidney Disease |
| Nephrotic Syndrome |
| Inflammation |
| Hypothyroidism |
| Acromegaly |
| Polycystic ovary syndrome |
| Growth hormone therapy |
| Androgen deprivation therapy |
| Statins |

In a patient with an elevated LDL-C level, one should take a diet history, review the medication list, and check a TSH level to rule out hypothyroidism. Most of the disorders that cause elevations in LDL-C levels,

other than hypothyroidism, should be obvious on routine history, physical examination, and laboratory screening. In a patient with an elevated triglyceride level, one should take a diet history and in particular

focus on the ingestion of simple sugars and ethanol. One should review the medication list and recognize that many common disease states can adversely impact triglyceride levels including obesity, poorly controlled diabetes, chronic renal failure, HIV, and inflammatory disorders (4,6-9). Weight loss, improvements in glycemic control in patients with diabetes, and a reduction of inflammation can all result in a decrease in triglyceride levels (4,6,7). In a patient with a low HDL-C level one should review the medication list and diet, recognizing that diets very low in fat can result in low HDL-C levels, which are often accompanied by low LDL-C and triglyceride levels (10). In young or very fit males with very low HDL-C levels a careful history directed at anabolic steroid use is essential (3).

THINK ABOUT GENETIC CAUSES

One should always consider the possibility of a genetic disorder and therefore ask whether relatives have

either premature cardiovascular disease, lipid disorders, or are taking lipid lowering medications (11). If the triglyceride levels are markedly elevated one should inquire about a family history of pancreatitis. When the lipid/lipoprotein abnormality is markedly abnormal or begins at a young age, the likelihood of a genetic disorder is increased and the family history assumes even greater importance. It is essential to think about the possibility of a genetic disorder because many of the common lipid disorders, such as familial hypercholesterolemia and elevations in Lp(a), have an autosomal codominant genetic transmission and therefore will be present in approximately 50% of family members (12-15). The recognition of the possibility of a genetic disorder will lead to screening family members and if abnormalities are found early treatment can be initiated, which may prevent the adverse consequences of hyperlipidemia. The monogenetic disorders that cause elevations in LDL-C and triglycerides levels and low HDL-C levels are shown in tables 8-11.

Table 8. Elevation in LDL Cholesterol (Familial Hypercholesterolemia)

| | | |
|--|----------------------|-------------------|
| LDL receptor mutations | Autosomal codominant | Approx. 1 in 250 |
| Apolipoprotein B mutations | Autosomal codominant | Approx. 1 in 1000 |
| PCSK9 mutations | Autosomal codominant | rare |
| Autosomal recessive hypercholesterolemia | Autosomal recessive | rare |
| Lysosomal acid lipase deficiency | Autosomal recessive | rare |
| Cholesterol 7 alpha hydroxylase deficiency | Autosomal recessive | rare |
| Sitosterolemia (ABCG5/ABCG8) | Autosomal recessive | rare |

In autosomal codominant disorders heterozygotes have lipid abnormalities approximately half as severe as homozygotes

Table 9. Marked Elevations in Triglycerides (Familial Chylomicronemia Syndrome)

| | | |
|---------------------------------------|---------------------|------|
| Lipoprotein lipase deficiency | Autosomal recessive | rare |
| Apolipoprotein C-II deficiency | Autosomal recessive | rare |
| Apolipoprotein A-V deficiency | Autosomal recessive | rare |
| GPIHBP1 deficiency | Autosomal recessive | rare |
| Lipase maturation factor 1 deficiency | Autosomal recessive | rare |

Table 10. Elevations in Triglycerides and Cholesterol

| | | |
|---------------------------------|------------------------------------|----------|
| Familial Dysbetalipoproteinemia | Apo E2/E2, rare mutations in Apo E | 1-5/5000 |
|---------------------------------|------------------------------------|----------|

Table 11. Decreased HDL Cholesterol

| | | |
|---|----------------------|------|
| Apolipoprotein A-I deficiency or variants | Autosomal codominant | rare |
| Tangier disease (ABCA1 deficiency) | Autosomal codominant | rare |
| LCAT deficiency | Autosomal codominant | rare |

In autosomal codominant disorders heterozygotes have lipid abnormalities approximately half as severe as homozygotes

Very frequently hypertriglyceridemia and/or hypercholesterolemia are due to polygenic inheritance secondary to combinations of common small effect genes that regulate the production or catabolism of lipoproteins (16). In addition, lifestyle, other disease states, and medications can interact with genetic susceptibilities to result in marked dyslipidemia and therefore even when a genetic disorder is present one should not ignore reversible factors where appropriate treatment can have marked effects on lipid levels. Often secondary factors facilitate the expression of genetic variations to result in an abnormal lipid phenotype. One of the best examples of the interaction of secondary factors and genetic variants is familial dysbetalipoproteinemia (17,18). The apolipoprotein E2/E2 polymorphism occurs in approximately 1% of individuals whereas the clinical disorder only occurs in 1-5/5000 and is frequently associated with other disorders, such as obesity, hypothyroidism, and diabetes, which also perturb lipid metabolism (17,18). A detailed discussion of the genetic disorders that effect plasma lipid and lipoprotein levels can be found in the individual Endotext chapters that focus on these disorders.

ORDERING SPECIAL LABORATORY STUDIES

In most circumstances a routine lipid panel consisting of triglycerides, total cholesterol, HDL-C, and calculated LDL-C and non-HDL-C provides sufficient information to appropriately decide on who to treat and the best treatment approach. In a patient with high fasting triglycerides (>200-400mg/dl) where the LDL-C cannot be accurately calculated measurement of direct LDL-C maybe very helpful. However, it should be recognized that there are certain situations where more sophisticated and detailed laboratory studies can be helpful (19). For example, in a young patient with atherosclerotic vascular disease and no obvious risk factors and a normal lipid profile obtaining specialized lipid/lipoprotein studies including measurement of Lp(a) would be indicated. Indications for measuring Lp(a) are shown in Table 12 (19,20). Note, it is the opinion of some experts that Lp(a) should be measured once in all individuals. The various specialized lipid and lipoprotein studies and their appropriate use are discussed in detail in the Endotext chapter "Utility of Advanced Lipoprotein Testing in Clinical Practice" (19).

Table 12. When to Measure Lp(a) Levels

| |
|---|
| Patients with premature CHD |
| Patients with a strong family history of premature CHD |
| Patients with a family history of elevated Lp(a) levels (Cascade screening) |
| Patients with resistance to LDL-C lowering with statins |
| Patients with familial hypercholesterolemia |
| Patients with aortic valvular stenosis of uncertain cause |
| Patients with an unknown cause of ischemic stroke |
| Patients with intermediate risk profiles |

Note: It is the opinion of some experts that Lp(a) should be measured once in all individuals

DECIDING WHO TO TREAT

The purpose of treating lipid disorders is to prevent the development of other diseases, particularly cardiovascular disease. Thus, the decision to treat should be based on the risk of the hyperlipidemia leading to those medical problems. A number of guidelines have been published that discuss in detail cardiovascular risk assessment and provide recommendations on treatment strategies (21-24). It should be noted that while these guidelines are similar there are significant differences between their recommendations. Additionally, several calculators are available on-line to determine an individual patient's risk of developing cardiovascular disease in the next 10 years or their lifetime risk. These issues are discussed in detail in the chapters on Risk Assessment and Guidelines for the Management of High Blood Cholesterol and Triglycerides (25-27). In addition to cardiovascular complications, marked elevations in triglycerides can lead to pancreatitis (26). The National Lipid Association recommends treating triglyceride levels greater than 500mg/dl while the Endocrine Society recommends treating triglycerides if they are greater than 1000mg/dl to lower the risk of pancreatitis (28,29).

GOALS OF THERAPY

The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not emphasize specific lipid/lipoprotein goals of therapy but rather to just treat with the statins to lower LDL-C by a certain percentage (21). An exception is that they do recommend in patients with very high-risk ASCVD, to use an LDL-C threshold of 70 mg/dL to consider addition of non-statins to statin therapy. In contrast, other groups, such as the National Lipid Association, International Atherosclerosis Society, European Society of Cardiology/European Atherosclerosis Society, and AACE, do recommend lowering the LDL and non-HDL cholesterol levels to below certain levels depending upon the cardiovascular risk in a particular patient but the recommendations from these organizations are not identical (22,24,29,30).

A detailed discussion of lipid/lipoprotein goals is provided in the chapter on Risk Assessment and Guidelines for the Management of High Blood Cholesterol (25). It should be noted that many lipid experts would recommend trying to achieve an LDL-C levels less than 70mg/dl and non-HDL-C levels less than 100mg/dl in patients with cardiovascular disease

or patients at very high risk for the development of cardiovascular disease. In other patients, an LDL-C level less than 100mg/dl and non-HDL-C level less than 130mg/dl is a reasonable goal. AACE and European Society of Cardiology/European Atherosclerosis Society have recommended LDL-C levels less than 55mg/dl in patients at very high risk (22,24). With the results of the IMPROVE-IT trial and PCSK9 inhibitor studies, which showed that adding ezetimibe or a PCSK9 inhibitor to statin therapy resulted in an additional decrease in LDL-C levels and a further reduction in cardiovascular events, the arguments in favor of trying to reach lower lipid/lipoprotein goals has been greatly strengthened (31-33). Moreover, the results of these and other studies provide strong support that the lower the LDL-C level the greater the reduction in cardiovascular events (34,35).

TREATMENT TO REDUCE COMPLICATIONS OF DYSLIPIDEMIA

The first priority in treating lipid disorders is to lower the LDL-C levels to goal, unless triglycerides are markedly elevated (> 500-1000mg/dl), which increases the risk of pancreatitis. LDL-C is the usual first priority because the data linking lowering LDL-C

with reducing cardiovascular disease are extremely strong and we now have the ability to markedly decrease LDL-C levels. Dietary therapy is the initial step but in the majority of patients' dietary modifications will not be sufficient to achieve the LDL-C goals. If patients are willing and able to make major changes in their diet it is possible to achieve remarkable reductions in LDL-C levels but this seldom occurs in clinical practice. Additionally, the dietary changes need to be sustained for a long period of time to be effective and many patients while able to follow an LDL-C lowering diet in the short term are unable to follow the diet for an extended period of time.

Primary Prevention Patients

The first step is determining the risk for developing atherosclerotic cardiovascular disease. There are a number of different calculators for determining risk. In the US the most popular is the ACC/AHA risk calculator (<http://www.cvriskcalculator.com/>) whereas in Europe the SCORE (Systematic Coronary Risk Estimation) is popular ([SCORE2 and SCORE2-OP \(escardio.org\)](http://score2.escardio.org)). The ACC/AHA recommendations are shown in Figure 1 and the European Society of Cardiology/European Atherosclerosis Society recommendations are shown in Figure 2.

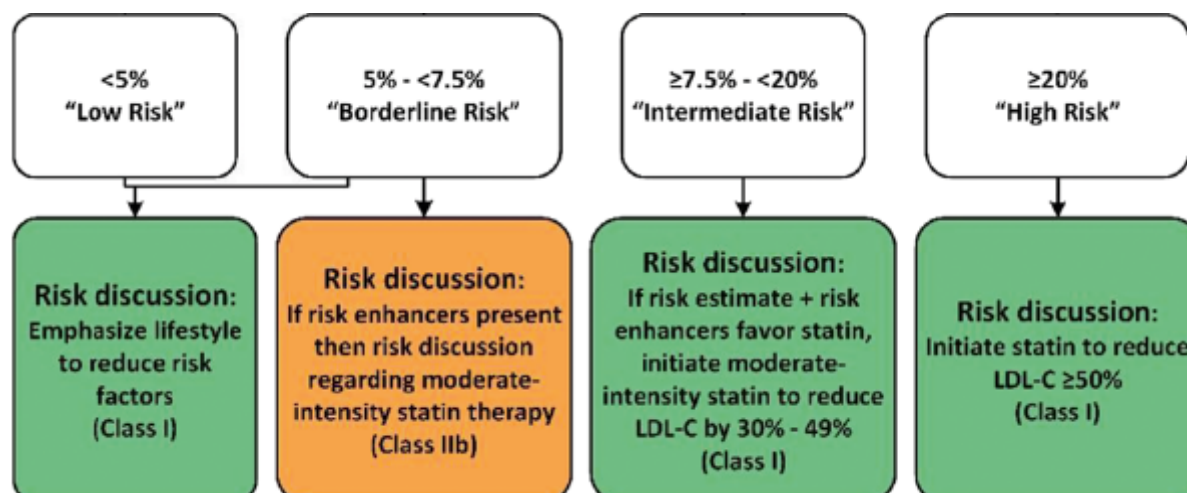


Figure 1. ACC/AHA Recommendations for Patients without ASCVD, Diabetes, or LDL-C greater than 190mg/dl. Risk enhancers are listed in table 13. (Note the risk is for MI and stroke, both fatal and nonfatal).

| Table 13. ASCVD Risk Enhancers |
|---|
| <p>Family history of premature ASCVD</p> <p>Persistently elevated LDL > 160mg/dl</p> <p>Chronic kidney disease</p> <p>Metabolic syndrome</p> <p>History of preeclampsia</p> <p>History of premature menopause</p> <p>Inflammatory disease (especially rheumatoid arthritis, psoriasis, HIV)</p> <p>Ethnicity (e.g., South Asian ancestry)</p> <p>Persistently elevated triglycerides > 175mg/dl</p> <p>Hs-CRP > 2mg/L</p> <p>Lp(a) > 50mg/dl or >125nmol/L</p> <p>Apo B > 130mg/dl</p> <p>Ankle-brachial index (ABI) < 0.9</p> |

| Total CV risk (SCORE) % | | Untreated LDL-C levels | | | | | |
|-------------------------|---|------------------------|--|--|--|--|--|
| | | <1.4 mmol/L (55 mg/dL) | 1.4 to <1.8 mmol/L (55 to <70 mg/dL) | 1.8 to <2.6 mmol/L (70 to <100 mg/dL) | 2.6 to <3.0 mmol/L (100 to <116 mg/dL) | 3.0 to <4.9 mmol/L (116 to <190 mg/dL) | ≥4.9 mmol/L (≥190 mg/dL) |
| Primary prevention | <1, low-risk | Lifestyle advice | Lifestyle advice | Lifestyle advice | Lifestyle advice | Lifestyle intervention, consider adding drug if uncontrolled | Lifestyle intervention and concomitant drug intervention |
| | Class ^a /Level ^b | I/C | I/C | I/C | I/C | IIa/A | IIa/A |
| | ≥1 to <5, or moderate risk (see Table 4) | Lifestyle advice | Lifestyle advice | Lifestyle advice | Lifestyle intervention, consider adding drug if uncontrolled | Lifestyle intervention, consider adding drug if uncontrolled | Lifestyle intervention and concomitant drug intervention |
| | Class ^a /Level ^b | I/C | I/C | IIa/A | IIa/A | IIa/A | IIa/A |
| | ≥5 to <10, or high-risk (see Table 4) | Lifestyle advice | Lifestyle advice | Lifestyle intervention, consider adding drug if uncontrolled | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention |
| | Class ^a /Level ^b | IIa/A | IIa/A | IIa/A | IIa/A | IIa/A | IIa/A |
| | ≥10, or at very-high risk due to a risk condition (see Table 4) | Lifestyle advice | Lifestyle intervention, consider adding drug if uncontrolled | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention |
| | Class ^a /Level ^b | IIa/B | IIa/A | IIa/A | IIa/A | IIa/A | IIa/A |

Figure 2. European Society of Cardiology/European Atherosclerosis Society Recommendations for Primary Prevention Patients. Risk categories are shown in table 14. (Note that the SCORE risk is for a fatal event). There are different tables for different European countries.

| Table 14. Cardiovascular Risk Categories | |
|---|--|
| Very High Risk | ASCVD DM with target organ damage or at least three major risk factors or early onset of T1DM of long duration (>20 years) Severe CKD (eGFR <30 mL/min/1.73 m ²) A calculated SCORE >10% for 10-year risk of fatal CVD FH with ASCVD or with another major risk factor |
| High Risk | Markedly elevated single risk factors, in particular TC >310 mg/dL, LDL-C >190 mg/dL, or BP >180/110 mmHg Patients with FH without other major risk factors Patients with DM without target organ damage with DM duration >10 years or another additional risk factor Moderate CKD (eGFR 30-59 mL/min/1.73 m ²). A calculated SCORE >5% and <10% for 10-year risk of fatal CVD |
| Moderate Risk | Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors Calculated SCORE >1 % and <5% for 10-year risk of fatal CVD. |
| Low Risk | Calculated SCORE <1% for 10-year risk of fatal CVD |

A few caveats are worth noting. First, in patients less than 60 years of age it is very helpful to calculate the life-time risk of ASCVD events. Often one will find that the 10-year risk is modest but the life-time risk is high and this information should be included in the risk discussion to help in the decision process. Second, patients should be made aware of the natural history of ASCVD i.e., that it begins early in life and slowly progresses overtime with high LDL-C levels accelerating the rate of development of atherosclerosis and low LDL-C leading to a slower progression of atherosclerosis (35,36). Third, patients should be made aware of genetic studies demonstrating that variants in genes that lead to lifetime decreases in LDL-C levels (for example the HMG-CoA reductase gene, NPC1L1 gene, PCSK9 gene, ATP citrate lyase gene, and LDL receptor gene) result in a decreased risk of cardiovascular events. In a recent study it was reported that a 10mg/dL lifetime decrease in LDL-C with any of these genetic variants was associated with a 16-18% decrease in cardiovascular events whereas a 10mg/dl reduction in LDL-C with lipid lowering therapy results in only

approximately a 5% decrease in cardiovascular events (34,37,38). The combination of the natural history and the results observed with genetic variants strongly suggests that early therapy to lower LDL-C levels will have greater effects on reducing the risk of ASCVD events than starting therapy later in life. This information needs to be discussed with the patient. Fourth, if the patient or health care provider are uncertain of the best course of action obtaining a cardiac calcium scan can be very helpful in the decision-making process, particularly in older individuals. A score of 0, particularly in an older patient would indicate that statin therapy is not needed whereas a score > 100 would indicate a need for statin therapy (21). A score of 1-99 favors the use of a statin (21).

In most primary prevention patients, statin therapy is sufficient to lower LDL-C levels to goal (< 100mg/dl). One can usually start with moderate statin therapy (for example atorvastatin 10-20mg or rosuvastatin 5-10mg) and increase the statin dose, if necessary, to achieve LDL-C goals. Statins are available as generic

drugs and therefore are relatively inexpensive. If a patient does not achieve their LDL-C goal on intensive statin therapy, cannot tolerate statin therapy, or is able to take only a low dose of a statin one can use ezetimibe (generic drug), bempedoic acid, bile acid sequestrants, or PCSK9 inhibitors to further lower LDL-C levels (for detailed discussion of cholesterol lowering drugs see (39)). It should be noted that the addition of ezetimibe or a PCSK9 inhibitor to statin therapy has been shown to reduce cardiovascular events (31-33). In most situations, ezetimibe is the drug of choice given its low cost, ability to reduce ASCVD events, and long-term safety record. If LDL-C is not close to goal PCSK9 inhibitors can be used. Once LDL-C is at goal if the non-HDL-C remains high one can consider the approaches described in the section describing the approach to patients with LDL-C at goal with elevated triglycerides.

Patients with LDL Cholesterol Greater than 190mg/dl

When the LDL-C is greater than 190mg/dl the patient should be started on intensive statin therapy (atorvastatin 40-80mg per day or rosuvastatin 20-40mg per day). If the LDL-C goal is not achieved (usually < 100mg/dl) additional lipid lowering medications should be added. If the LDL-C is relatively

close to goal one can use ezetimibe but if the LDL-C is far from the goal the use of a PCSK9 inhibitor should be employed. Because of the potential for a genetic disorder, either monogenic or polygenic, one should check family members for lipid abnormalities. If possible genetic testing for monogenic disorders causing hypercholesterolemia is recommended (40).

Patients with Diabetes

Most patients with diabetes (age 40-75) without risk factors should be started on moderate statin therapy (for example atorvastatin 10-20mg or rosuvastatin 5-10mg). In young individuals (< age 40) and older individuals (> age 75) one needs to use clinical judgment. Patients with diabetes with ASCVD or risk factors should be started on intensive statin therapy. In my opinion reasonable goals are shown in table 15 (similar to AACE and ADA guidelines) (24,41). If intensive statin therapy does not achieve LDL-C goals additional drugs can be added. If reasonably close to the LDL-C goal the initial drug added should be ezetimibe. If far from goal one could add a PCSK9 inhibitor. Once LDL-C is at goal if the non-HDL-C remains high one can consider the approaches described in the section describing the approach to patients with LDL-C at goal with elevated triglycerides.

Table 15. ASCVD Risk Categories and Treatment Goals

| Risk Category | Risk Factors/10-year risk | LDL-C mg/dl | Non-HDL-C mg/dl |
|----------------------|--|--------------------|------------------------|
| Extreme Risk | Diabetes and clinical cardiovascular disease | <55 | <80 |
| Very High Risk | Diabetes with one or more risk factors | <70 | <100 |
| High Risk | Diabetes and no other risk factors | <100 | <130 |

Secondary Prevention Patients

Patients with ASCVD (secondary prevention patients) should be started on intensive statin therapy (atorvastatin 40-80mg per day or rosuvastatin 20-40mg per day). Given the extensive data showing that the lower the LDL-C the greater the reduction in ASCVD events most secondary prevention patients would benefit from the addition of ezetimibe to maximize LDL-C lowering without markedly increasing costs (34,35). The goal LDL-C in this patient population is an LDL-C<70mg/dl but many experts and some guidelines would prefer an LDL-C<55mg/dl if possible. If on intensive statin therapy and ezetimibe treatment the LDL-C is far above goal one could consider adding a PCSK9 inhibitor (this is particularly necessary if the LDL-C is greater than 100mg/dl or the patient is at very high risk due to other factors (diabetes, cerebral vascular disease, peripheral vascular disease, recent MI, history of multiple MIs) (34,35).

Patients with LDL Cholesterol at Goal but High Triglycerides (>150mg/dl to <500mg/dl)

Patients with an LDL-C at goal but high triglyceride levels (>150mg/dl to <500mg/dl) will often have increased non-HDL-C levels. Numerous studies have shown that the risk of ASCVD events is increased in this patient population (42). The initial step should be to improve lifestyle, treat secondary disorders that may be contributing to the increase in triglycerides, and if possible, discontinue medications that increase triglyceride levels. Studies have not demonstrated a reduction in cardiovascular events when niacin is added to statin therapy and given the side effects of niacin enthusiasm for using niacin in combination with statins to reduce ASCVD is limited (43,44). Additionally, the ACCORD-LIPID trial failed to demonstrate that adding fenofibrate to statin therapy (45) and the PROMINENT trial failed to demonstrate

that adding pemafibrate to statin therapy (46) reduces cardiovascular disease. Thus, there is little evidence that adding either niacin or a fibrate to statin therapy will be beneficial in reducing cardiovascular events.

The REDUCE-IT trial demonstrated that adding the omega-3-fatty acid icosapent ethyl (EPA; Vascepa) to statin therapy in patients with elevated triglyceride levels reduced the risk of ASCVD events by 25% while decreasing triglyceride levels by 18% (47). Similar results were seen in the JELIS trial (48). In these trials the reduction in triglyceride levels was relatively modest and would not have been expected to result in the magnitude of the decrease in cardiovascular disease observed in the JELIS and REDUCE-IT trials. Other actions of EPA, such as decreasing platelet function, anti-inflammation, decreasing lipid oxidation, stabilizing membranes, etc. could account for or contribute to the reduction in cardiovascular events (49). Based on these results the National Lipid Association has recommended “that for patients aged ≥ 45 years with clinical ASCVD, or aged ≥ 50 years with diabetes mellitus requiring medication plus ≥ 1 additional risk factor, with fasting TGs 135 to 499 mg/dL on high-intensity or maximally tolerated statin therapy (\pm ezetimibe), treatment with icosapent ethyl is recommended for ASCVD risk reduction” (50). However, it should be recognized that the STRENGTH trial using a carboxylic acid formulation of EPA and DHA failed to reduce cardiovascular events despite reducing triglyceride levels to a similar degree as in the REDUCE-IT trial (51). Whether EPA has special properties that resulted in the reduction in cardiovascular events in the REDUCE-IT trial or there were flaws in the trial (the use of mineral oil as the placebo) is debated (49,52). For a detailed discussion of triglyceride lowering drugs see the Endotext chapter on this topic (53).

Patients with Very High Triglyceride Levels (>500-1000mg/dl)

The main aim is to keep triglyceride levels below 500 mg/dL to prevent triglyceride-induced pancreatitis (17,54,55).

FAMILIAL HYPERCHYLOMICRONEMIA (FCS)

FCS is a rare autosomal recessive disorder due to an abnormality in the genes listed in table 9 that result in the absence of functional lipoprotein lipase (LPL) activity (17,54,55). Patients with FCS respond poorly to most triglyceride lowering drugs (fibrates, omega-3-fatty acids, niacin) (17,54,55). A very low-fat diet (5-10% of total calories) is the most effective treatment but can be difficult for many patients to comply with (17,54,55). Volanesorsen, a drug that is approved in Europe but not in the US, lowers ApoC-III levels and is effective in lowering triglyceride levels in patients with FCS (53).

MULTIFACTORIAL CHYLOMICRONEMIA SYNDROME (MCS)

MCS is due to the coexistence of a genetic predisposition (polygenic or heterozygous for genes that cause FCS) to hypertriglyceridemia with 1 or more secondary causes of hypertriglyceridemia (see tables 3 and 4) (17,54,55). Initial treatment is a very low-fat diet to reduce triglyceride levels into a safe range (<1000mg/dl). Treating secondary disorders that raise

triglyceride levels and when possible, stopping drugs that increase triglyceride levels is essential (17,54,55). If the triglyceride levels remain above 500mg/dl the addition of fenofibrate or omega-3-fatty acids is indicated. Many patients with MCS are at high risk for ASCVD and therefore after triglyceride levels are controlled the patient should be evaluated for cardiovascular disease risk and if indicated statin therapy initiated.

Patients with High Lp(a) Levels

Life style changes do not significantly lower Lp(a) levels (56). The effect of lipid lowering drugs on Lp(a) levels is shown in Table 16. In patients with elevations in Lp(a) the initial therapy is to aggressively control the other cardiovascular disease risk factors. In some instances, one can use niacin, PCSK9 inhibitors, or in postmenopausal women estrogen to lower Lp(a) levels but the effect of these drugs on preventing cardiovascular events by lowering Lp(a) levels is uncertain (57). Studies of an antisense oligonucleotide or small interfering RNA (both not yet approved) directed at apo(a) have shown that these drugs can lower Lp(a) by >75% without effecting other lipoprotein levels (58). Lipoprotein apheresis can be employed to lower Lp(a) in patients with very high Lp(a) levels who continue to have cardiovascular events despite optimal medical management (59).

Table 16. Effect of Lipid Lowering Drugs on Lp(a) Levels

| | |
|---------------------|--|
| Statins | No Effect or slight increase |
| Ezetimibe | No Effect or slight increase |
| Fibrates | No Effect |
| Niacin | Decrease 15-25%. Greatest decrease in patients with highest Lp(a) levels |
| PCSK9 Inhibitors | Decrease 20-30% |
| Estrogen | Decrease 20-35% |
| Mipomersen** | Decrease 25-30% |
| Lomitapide* | Decrease 15-20% |
| Evinacumab | No effect in homozygous familial hypercholesterolemia Decrease 16% in refractory hypercholesterolemia |
| CETP Inhibitors** | Decrease ~ 25% |
| Apo (a) antisense** | Decrease > 75% |

*only approved for the treatment of Homozygous FH; **not currently available

Decreased HDL Cholesterol Levels

Despite epidemiologic studies consistently showing that high HDL-C levels are associated with a decreased risk of cardiovascular disease there are no studies demonstrating that increasing HDL-C levels reduces cardiovascular disease (60). It should be recognized that the crucial issue with HDL may not be the HDL-C levels per se but rather the function of the HDL particles (60). Assays have been developed to determine the ability of HDL to facilitate cholesterol efflux from macrophages and these studies have shown that the levels of HDL-C do not necessarily indicate the ability to mediate cholesterol efflux (61).

Similarly, the ability of HDL to protect LDL from oxidation may also play an important role in the ability of HDL to reduce ASCVD (62). Thus, the functional capability of HDL may be more important than HDL-C levels (60-62).

CONCLUSION

In summary, modern therapy demands that we aggressively evaluate and when indicated treat lipid disorders to reduce the risk of atherosclerotic cardiovascular disease and in those with very high triglycerides to reduce the risk of pancreatitis.

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