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Lipid Targets and Cardiovascular Risk

Introduction: The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) provides guidelines for cholesterol lowering management based on the patient's risk category. The most recent guidelines for cholesterol lowering were published in 2001 and updated in 2004. The update added an additional risk category (very high risk) and added an optional target LDL-cholesterol of <70mg/dl for very high risk patients. Also, non HDL-C became a secondary target for therapy if triglycerides where >200mg/dl. The non HDL-cholesterol (non HDL-C) target was lowered from 130mg/dl to 100mg/dl for very high risk patients. For all other risk categories the target values remained the same.

Since 2004, the previously designated 'emerging risk factors', which also determine risk and targets of therapy, are now in common use. For example, the high sensitivity C-reactive protein (done routinely at Rex Lab) helps identify those who are likely at high cardiovascular risk. Lab tests done in reference labs such as tests for LDL-particle (LDL-P) count by nuclear magnetic resonance, apolipoprotein B (apo B) concentrations and Lipoprotein-a [Lp(a)] are increasing in importance for risk assessment. In addition the imaging modalities that determine carotid artery intima-media thickness (CIMT) by ultrasound and the coronary artery calcium score (CAC) by CT are commonly used to uncover subclinical atherosclerosis.
In the following paragraphs, I will review the methods of determining cardiovascular (CV) risk, the lab tests used and targets for lipid therapy.

The risk category determines the lipid target value: A patient's cardiovascular risk is determined by clinical judgment and standardized major risk factors. According to the ATP III algorithm, persons are categorized into three risk categories: 1) established coronary heart disease (CHD) and CHD risk equivalents, 2) multiple (2+) risk factors and 3) zero to one (0–1) risk factor. CHD risk equivalents include non-coronary forms of clinical atherosclerotic disease, diabetes and multiple (2+) CHD risk factors with 10-year Framingham risk for CHD ≥20%. All persons with CHD or CHD risk equivalents can be called high risk. Table 1 shows the risk categories and the corresponding target values for LDL-cholesterol and non HDL-cholesterol.

Framingham Risk Score: The Framingham risk score in conjunction with the major risk factors are recommended to assess CV risk (see Table 2). The ATPIII has a website that allows downloading of an excel based spreadsheet or Palm application to calculate the Framingham risk score (http://hp2010.nhlbihin.net/atpiii/riskcalc.htm or http://nhlbi.nih.gov). Even though the ATP III recommends using the Framingham 10 year risk score, busy clinicians frequently determine cardiovascular risk by clinical judgment rather than by calculating the Framingham 10 year risk score for each patient. It is important to remember that the Framingham risk score is not valid if the patient is taking lipid lowering medication. Depending on the clinical setting, cardiovascular risk may be assessed by ordering a CIMT or CAC to diagnose subclinical atherosclerosis. Evidence of disease found using these imaging modalities is justification for more aggressive therapy.

Table 1: Target Values of Therapy (NCEP ATP III 2004)

Risk level	Patient profile	LDL-C target mg/dl	Non-HDL-C target mg/dl
Low	No CHD, 0-1 risk factor	<160	<190
Moderate	No CHD, 2+ risk factors plus (10-year risk <20%)[1]	<130	<160
High Very High	CHD or equivalents plus (10-year risk ≥20%)[1]	<100 <70 optional*	<130 <100 optional

Primary target = LDL-C; Secondary target = Non HDL-C (if Trigs >200);
[1] Framingham 10 year risk percentage for CV event
***Optional = those considered very high risk**

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Table 2: Major Cardiovascular Risk Factors

- Age: male >45 years, female >55 years
- HDL cholesterol <40 mg/dl
- Active smoking (in the past month)
- Hypertension (≥140/90 or taking antihypertensive medication)
- Family history of premature heart disease; age <55 male or age <65 female

(Modified from PocketGuide – Lipid and Lipoprotein disorders[2])

Metabolic Syndrome: The NCEP popularized the term metabolic syndrome (also known as insulin resistance). A clue to this high risk clinical syndrome is a distinctive body type with increased abdominal circumference as a result of increased visceral fat. Although most individuals with metabolic syndrome have abdominal obesity, relatively thin people may also meet the criteria. Even though insulin resistance is at the core of the factors that comprise this syndrome, there probably is a multifactorial etiology resulting from:

- Abdominal (visceral) obesity
- Physical inactivity
- High intake of calories and saturated fat.

Waist circumference, measured at the iliac crest and parallel to the floor, is more important than total weight or body mass index in the diagnosis of metabolic syndrome. For the diagnosis of the metabolic syndrome, three of the five criteria listed in the metabolic syndrome table (Table 3) are necessary. The most important therapy for metabolic syndrome is diet and exercise.

Table 3: Metabolic Syndrome risk factors [1]

Risk Factor	Cut-point
Abdominal Obesity	Waist circumference
Men	≥ 40 inches (≥ 35 inches in Asian men)
Women	≥ 35 inches (≥ 32 inches in Asian women)
HDL-C2	
Men	≤ 40 mg/dl
Women	≤ 50 mg/dl
Triglycerides[2]	≥ 150 mg/dl
Blood Pressure[2]	≥ 130/ ≥ 85 mmHg
Fasting blood glucose[2]	≥ 100 mg/dl

[1]The presence of 3 or more risk factors constitutes a diagnosis of metabolic syndrome.
[2]The risk factor is considered positive if the patient is on medication for the marker.
(Modified from PocketGuide – Lipid and Lipoprotein disorders[2])

Lipoproteins are vehicles in the plasma: Lipoproteins are tiny spheres that circulate in the plasma and are composed of a lipid and aqueous component. They include very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL), Lipoprotein a (Lp(a) – "L-p-little a"), VLDL remnants and high density lipoproteins (HDL). Cholesterol is carried in the plasma within the core of lipoprotein particles (see Figure 1). High density lipoproteins (HDL) contain apolipoprotein A on the surface and are not atherogenic. On the other hand, LDL has apolipoprotein B on the surface and is atherogenic. The cholesterol and triglyceride content of the lipoproteins is in constant flux. The proportion of each lipid in the core is determined by many variables including diet and genetics. All lipoproteins containing apo B are capable of forming plaque by entering the endothelial lining of vessels.

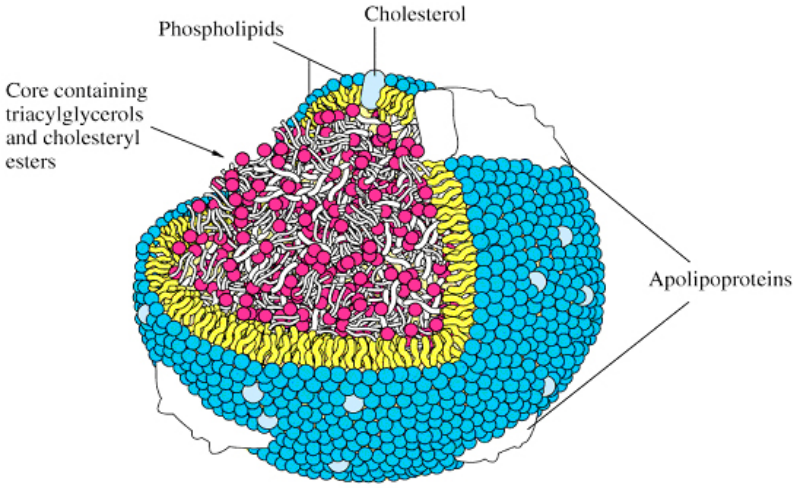

Figure 1 Lipoprotein particle. Note: cholesterol and triglycerides are carried in the core of the particle. (chienlab.wikispaces.com)

LDL-C; the primary target for therapy: LDL-cholesterol (LDL-C) is the measurement of the cholesterol content in the LDL particles (LDL-P) circulating in the plasma. For twenty years LDL-C has been the primary target for lipid lowering therapy. Lowering the LDL-C has decreased cardiovascular events 20 to 30% in adequately treated individuals. However, patients continue to have events in spite of achieving the LDL-C goal. In most clinical labs and at the Rex lab, LDL-C is usually calculated by the Friedewald formula. After directly measuring total cholesterol (TC), triglycerides (TRIG) and HDL cholesterol (HDL-C) on a fasting specimen, the LDL-C is calculated (LDL-C=TC-HDL-C-1/5TRIG). Calculating the LDL-C provides a reasonable estimate but does not appear to be the best estimate of CV risk for those with metabolic syndrome and diabetes. However, measuring LDL-C directly, rather than the calculated LDL-C, does not improve determination of the true CV risk. In these patients the LDL-particle count and apo B levels are more predictive of risk.[10-12]

There are many patients with low levels of LDL-C (thought to be at goal) that have a high number of LDL P. These patients commonly have small dense LDL-P. Patients with a low LDL-C but high numbers of LDL-P, have an increased cardiovascular risk.[3]

Non HDL-C; a secondary target for therapy: Non HDL cholesterol is a calculated parameter in the routine lipid profile. It is calculated from the total cholesterol minus HDL cholesterol. It is easy to calculate, does not require fasting and measures the cholesterol within all atherogenic particles including LDL. Non HDL-C is currently recognized by the NCEP ATPIII as a secondary target of therapy for those individuals with triglycerides >200mg/dl. The target value of non HDL-C is the target value of LDL-C plus 30.

Framingham data reveals that once non HDL-C target is achieved through therapy, LDL-C is no longer a risk factor (Am. Journal of Cardiology, 2006, 98:1363 1368). The non HDL-C may not be the best target or reflect the true risk of disease in certain patients, but based on recent literature, many experts believe it is a better marker than LDL-C.[9] Unfortunately, non HDL-C does not always reflect the true risk in patients with metabolic syndrome and diabetes. Again, in these patients the LDL-particle count and apo B levels are more predictive of risk.[10-12]

Apo B; another measurement of risk: Apolipoprotein B is found in VLDL, IDL, LDL, Lp(a), and VLDL remnants. Each of these lipoproteins contains one molecule and only one of apo B. Accordingly, apo B provides a direct measurement of the number of all atherogenic particles in the circulation. There are no apo B lipoproteins in HDL lipoproteins.

Apo B can be measured by an immunoassay of the plasma. Standardization of the immunoassay for apo B has made the assay more reproducible between clinical laboratories. When apo B, LDL-C and non HDL-C values were evaluated simultaneously in some large scale studies, relative risk was most strongly associated with apo B.[9] The Canadian Cardiovascular Society has made apo B a primary target of therapy.[13] The apo B target value of <90mg/dl is used for high risk patients and <80mg/dl for very high risk patients.

LDL particle count, another measurement of risk: LDL-particles represent >90% of the atherogenic lipoproteins circulating in plasma. Both large and small LDL particles are equally capable of forming atherosclerotic plaque. VLDL, IDL, and VLDL remnants are atherogenic but present in low concentrations. They have a short half life of only a few hours in the circulation. In contrast LDL is present in larger concentration with a half life of two to three days and therefore is responsible for the majority of risk. A direct measurement of the actual number of LDL P is a precise way to measure risk. As mentioned previously, LDL-C is a measurement of cholesterol within LDL-P. Variation in the size and the concentration of triglycerides within LDL-P impacts directly on the quantity of LDL-C in the core. The more triglycerides that are in the LDL-P core, the less the amount of LDL-C is present. Accordingly, LDL-C does not always reflect the LDL particle concentration (LDL-P).

Rosenson writes *"Among high cardiometabolic risk patients with LDL-C <100 mg/dl, about two-thirds of patients have a high LDL-P (>1,000 nmol/L) despite this 'optimal' level of LDL-C. For high cardiometabolic risk patients, LDL-P should be considered a primary goal of therapy due to its stronger association with cardiovascular risk."* [15] The cutpoint of <1,000 nmol/l of LDL-P is considered by most to be the target for high risk individuals. An optional goal of <750 nmol/L of LDL-P may be considered for selected very high risk patients in hopes of regression of plaque. In 2008 the American Diabetes Association and American College of Cardiologists recommended measuring apo B and/or LDL-P in assessing risk.[9]

Conclusion: Practicing physicians manage lipid abnormalities based on the evidence in the literature, clinical judgment and experience. The growing body of evidence suggests more advanced imaging modalities are capable of uncovering subclinical cardiovascular disease. It is likely that measuring carotid intima-media thickness by ultrasound and coronary artery calcium scores will become more prevalent and permit improved risk stratification. Considerable debate and controversy have developed regarding the relative merits of monitoring LDL in terms of cholesterol content or particle count. The recent literature shows apo B and LDL-particle concentration are clearly superior to LDL-C in evaluating risk and as a target of therapy.[4] Therapeutic life style changes remain the cornerstone of lipid management. In addition more aggressive combination therapy (statin plus niacin/fibrate and/or ezetimibe (zetia) are used more commonly in routine clinical practice.

The National Cholesterol Education Program (Adult Treatment Panel IV) will submit new guidelines for CV risk assessment and target values for monitoring therapy in 2011. The Committee's recommendation will set the standard for accessing risk and targets for therapy.

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