Novel Cholesterol Subtypes

Markers of Cardiovascular Risk

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Implementation of aggressive treatment targets for LDL-C has been credited with materially reducing risk of all cause death, sudden coronary death, stroke, as well as reduced risk of non fatal major coronary events, principally among populations of patients in settings of secondary coronary prevention. None-the-less, questions remain, notably the phenomena whereby many individuals suffering cardiovascular events do so while having very low levels of circulating LDL-C, the apparent failure of statin therapy to correct coronary artery calcification, and the controversy surrounding the role of statin therapy in settings of primary coronary prevention. A selection of novel lipid markers may be able to equip practitioners to better predict a patients cardiovascular risk; these markers may correct erroneous risk predictions based on LDL among a subset of patients for whom assessment of LDL-C has proven to be a poor predictor of risk, they may identify individuals at risk sooner than LDL assessment alone would detect risk, and they may show reduced risk among a subset of individuals with marginally elevated LDL-C, preventing over treatment. The following review will examine evidence surrounding the role of Lp-PLA2, Apo B, LDL-P, Lp(a), and LDL/HDL subfractions in predicting risk of cardiovascular events.

Introduction

Guidelines for cholesterol testing to examine cardiovascular (CV) risk have primarily relied on measurements of low-density lipoprotein cholesterol (LDL-C) and secondarily on non-high-density lipoprotein cholesterol (HDL-C) (NCEP 2002). Patients are stratified by CV risk and then LDL-C treatment goals are set based on their classification. This LDL-C strategy has been successful in reducing the incidence of CV morbidity and mortality. Further analyses of clinical trial data have supported the idea that non-HDL-C is a better treatment target than LDL-C (Robinson 2009). Non-HDL-C includes both LDL-C and VLDL-C and it is derived from calculating total cholesterol minus HDL-C. However, measurements and treatment to non-HDL-C goals have not been utilized, largely as a result of knowledge gaps on behalf of physicians (Virani 2011). Even though statins and LDL-C reduction reduce CV events, there remains a residual risk for events in both primary and secondary prevention populations. Primary prevention refers to avoiding the occurrence of disease. Secondary prevention refers to when disease is already present but before it causes significant morbidity. Residual risk is present in those who are on statin therapy and it is most evident in patients with metabolic syndrome and diabetes (Drexel 2010 & Rosenson 2010). As a result, the use of lipid biomarkers is a high-interest topic that has a large potential for clinical utility and to possibly improve patient outcomes. This is especially important as the availability of generic statins has decreased the cost of treatment and has improved the cost-effectiveness of using lipid markers (Davidson 2011). This article will review the recent assessment of an expert panel of lipid specialists in their analysis of the following lipid markers: lipoprotein-associated phospholipase A2 (Lp-PLA2), apolipoprotein (Apo) B, LDL particle concentration (LDL-P), lipoprotein(a) [Lp(a)], and LDL and HDL subfractions (Davidson 2011). The evaluation of novel markers can provide valuable insight into a patient's CV risk, especially where there is suspicion that a patient may be at higher risk than suggested by LDL-C alone.

"Focusing treatment goals on LDL-C has been successful in reducing the incidence of CV morbidity and mortality."

Current Guidelines

Many epidemiological studies have confirmed that the following risk factors account for the majority of coronary artery disease (CAD) cases: age, male gender, cigarette smoking, diabetes mellitus, cholesterol (as assessed by total cholesterol and LDL-C), HDL-C, elevated blood pressure, a family history of premature CAD before the age of 60, inflammatory biomarkers such as hs-CRP, and overweight or obesity (Smith 2006). Other variables that increase risk are poor nutrition, caloric excess, physical inactivity, and psychological stress. Current cholesterol treatment targets are obtained from the data of clinical trials. Most studies measure the serum or plasma of LDL-C. The Cholesterol Treatment Trialists meta-analysis of 14 statin trials showed a dose-dependent relative reduction in cardiovascular disease (CVD) with LDL-C lowering (Baigent 2005). The CTT Collaborators found that every 1.0 mmol/L reduction in LDL-C is associated with a corresponding 20% to 25% reduction in CVD mortality and nonfatal myocardial infarction. Secondary targets include a total cholesterol to HDL-C ratio of less than 4.0, a non-HDL-C level of less than 3.5 mmol/L, an Apo B/Apo AI ratio of less than 0.80, a triglyceride level of less than 1.7 mmol/L and an hs-CRP level of less than 2.0 mg/L (Genest 2009). The current guidelines advocate optimizing these secondary targets in high-risk patients only after achieving LDL-C targets.

Lp-PLA2

Lp-PLA2 circulates bound to LDL particles, HDL particles, Lp(a), and

triglyceride-rich remnant lipoproteins (Anderson 2008). It is produced by numerous cell types, including mast cells, macrophages, and liver cells (Braun 2010). Lp-PLA2 activity is up-regulated in atherosclerotic lesions and in rupture-prone fibrous caps (Koenig 2006). Lp-PLA2 is an enzyme responsible for the hydrolysis of oxidized phospholipids in LDL particles within the arterial intima and produces two highly inflammatory mediators (Anderson 2008). These mediators result in a cascade of events linked to atherosclerotic plaque formation, including the expression of cytokines and the production of foam cells (Braun 2010). Foam cells aggregate to form a fatty streak covered by a fibrous cap, while cytokines and proteases destroy the collagen within the fibrous cap, making it prone to rupture (Davidson 2011).

Lp-PLA2 levels have been identified as a significant predictor of CV events and stroke (Braun 2010). In primary and secondary prevention trials, patients with Lp-PLA2 in the upper tertile or upper quartile had an approximately 2-fold increase in risk for CV events (Anderson 2008). In addition, unlike LDL-C, epidemiological studies show that an elevation in Lp-PLA2 confers a 2-fold increase in both first and recurrent strokes (Gorelick 2008). A meta-analysis of 80,000 patients showed that Lp-PLA2 elevations caused an 8% to 16% relative risk increases in the following: coronary heart disease (CHD), ischemic stroke, and vascular mortality (Lp-LPA2 Collaboration 2010). Interestingly, omega-3 fatty acids and weight loss have been shown to reduce Lp-LPA2 (Tzotzas 2008).

Apo B

All triglyceride-rich lipoprotein particles secreted by the intestine or the liver have one molecule of Apo B (Elovson 1988). The Apo B encircles the particle, provides external structural integrity, and stays with the lipoprotein particle for its lifetime. Thus, plasma Apo B concentration is a direct indication of the total number of circulating Apo B-containing lipoprotein particles. Atherosclerosis is initiated and advanced by the trapping of Apo B-containing lipoprotein particles within the subintimal space of the arterial wall (Davidson 2011). LDL Apo B particles have a greater importance in driving atherosclerosis because they are in greater concentration than VLDL Apo B particles and are smaller so they can enter the arterial wall more readily. The more Apo B particles enter the arterial wall, the greater the increase in the number trapped in the subendothelial space, and this leads to the development and progression of atherosclerosis (Smith 1982).

LDL-C is not the best indicator of the risk attributable to LDL because risk correlates more closely with the number of circulating atherogenic particles than with the quantity of cholesterol carried by those particles (Ingelsson 2007). The amount of cholesterol per LDL particle varies significantly. To better understand the problem this creates, consider a patient whose LDL particles contain less cholesterol than normal. This patient will have LDL-C concentrations that will underestimate the number of LDL particles. In such a patient, the Apo B concentration will more accurately reflect the number of LDL particles and the LDL-related CV risk. Next, consider the reverse situation: a patient whose LDL particles contain more cholesterol than normal. In this patient, the LDL-C concentration will overestimate the number of LDL particles. In this case too, the Apo B concentration will provide a more accurate representation of LDL particles (Sniderman 2007). Cholesterol-poor LDL particles are the dominant form of LDL in a substantial portion of patients who are in all major clinical risk groups for vascular disease (Davidson 2011). In these groups, Apo B better reflects CV risk and this has been supported by a meta-analysis (Sniderman 2011). As a bonus, fasting is not required for Apo B measurement.

LDL-P

LDL particles can move into the arterial wall and the greater the circulating concentration of LDL particles, the greater the rate of passive diffusion into the arterial wall and the greater the vesicular ferrying through endothelial cells (Nielsen 1996). LDL particles bind to arterial wall proteoglycans, become oxidized, and are taken up by macrophages to form foam cells (Tabas 2007). When serum LDL-P is high, there are a greater amount of LDL particles in circulation and a greater amount of particles may enter the arterial wall. Conversely, when LDL-P is low, there are fewer LDL particles and a decrease in the initiation and promotion of atherosclerosis.

LDL-P represents the number of LDL particles and is therefore an alternative way to quantify LDL, as oppose to relying solely only on LDL-C. For many patients, their LDL-C and LDL-P are highly correlated. However, because of variability of the cholesterol content and size of LDL particles, they are sometimes unrelated (Otvos 2002). In the general population, approximately 50% of subjects have discordance between LDL-C and LDL-P (Otvos 2011). In those with elevated triglycerides or low HDL-C, the discordance rates are higher and the same is true of those with type 2 diabetes mellitus or metabolic syndrome (Cromwell 2007, Otvos 2011). CV risk is more strongly associated with LDL-P than with LDL-C when these two measures are discordant (Otvos 2011). LDL-P and Apo B are both measures of particle number. As such, the decision to use one or the other is determined by availability, cost, and physician preference.

Lp(a)

Lp(a) is a modified LDL molecule with the addition of a protein made in the liver, known as the lipoprotein antigen (Koschinsky 2004). The lipoprotein antigen is highly polymorphic in size, which causes highly variable molecular weights and variable plasma concentrations in the population (Kronenberg 1999). Lp(a) is taken up in the arterial wall by scavenger receptors on macrophages called beta-integrin Mac-1 (Sotiriou 2006). Interestingly, homocysteine increases the Mac-1 interaction with Lp(a) antigen by up to threefold. Lp(a) also binds to fibrin and may enhance the clotting triggered by endothelial damage or plaque rupture (Koschinsky 2004). The number of molecules of Lp(a) appear to be the strongest determinant of related CV risk (Davidson 2011).

When examining study data, Lp(a) has positive predictive power that is additive to other measures of lipoprotein risk factors (Davidson 2011). Lp(a) is specifically associated with increased risk for CHD in a continuous nonthreshold manner. The association between Lp(a) and CHD risk is independent of LDL-C, non-HDL-C, and the presence of other CV risk factors (Nordestgaard 2010). This makes Lp(a) a useful tool for assessing clinical risk, especially when there is a strong family history of vascular events, since elevated plasma concentrations are controlled by features of the Lp(a) gene (Kamstrup 2009).

LDL and HDL subfractions

Every lipoprotein particle in the LDL fraction is atherogenic, regardless of size. LDL particles become trapped in the arterial wall, cause foam cell formation, and cause the expansion of the inflammatory response (Ross 1999). HDL particles are involved in reverse cholesterol transport and also possess antiatherogenic properties, including antioxidant and anti-inflammatory properties (Rosenson 2011). Therefore, there is physiological rationale for the links between both LDL and HDL subfractions and adverse CV outcomes.

LDL particles vary in size, density, and cholesterol content. Small LDL particles are often present in patients with features of metabolic syndrome, including those with CHD, diabetes, low HDL and high triglycerides, and in those with insulin resistance (Sacks 2003). However, the statistical associations between small, dense LDL and CHD outcomes are diminished or disappear altogether when adjusted for LDL-P. Currently, there are no patient subgroups that have been identified in which LDL subfractionation has supporting evidence showing benefit (Sacks 2003). HDL particles are also variable in terms of size, charge, density, and cholesterol content. Many antiatherosclerotic functions of HDL are not fully understood (Reilly 2007). Population studies support the notion that HDL-C has protective effects for CV risk and HDL subfractions also correlate with this risk (Williams 2011). Similar to LDL subfractions, there have been no patient subgroups in which there is evidence supporting the routine use of HDL subfractionation.

Conclusion

Focusing treatment goals on LDL-C has been successful in reducing the incidence of CV morbidity and mortality. However, LDL-C does not adequately assess risk in all population subgroups due to the variability of multiple associated factors. As a result, the use of lipid biomarkers has large potential for clinical applications and could improve patient outcomes. This article reviewed the recent assessment of the expert panel of lipid specialists in their analysis of multiple lipid markers. Lp-PLA2 elevations were shown to cause 8% to 16% relative risk increases in CHD, ischemic stroke, and vascular mortality. Apo B was shown to better reflect CV risk in a substantial portion of patients, especially in those patients with other major clinical risks for vascular disease. LDL-P was shown to be more strongly associated with CV risk than LDL-C, especially in patients with elevated triglycerides or low HDL-C, in those with type 2 diabetes mellitus, and in those with metabolic syndrome. Apo B and LDL-P are both measures of particle number and the merits of choosing one over the other or using both are unclear. Lp(a) was shown to be specifically associated with increased risk for CHD in a continuous nonthreshold manner, independently of many other risk assessment parameters. Finally, LDL and HDL subfractions were shown to be weaker predictors of CV risk, despite physiologic rationale that appeared promising for both. Overall, many of these lipid markers appear to be useful in certain patient subgroups. However, some controversies exist on their value and it is difficult to recommend when they should be used, or for which patients they would be most beneficial. Beyond that, it may also be difficult to determine how these markers may impact specific treatment goals or specific treatment decisions. ■

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