

PRACTICAL LIPID MANAGEMENT AND THE ROLE OF ADVANCED LIPID TESTING

Scott J Deron, DO, FACC, FSCAI
Cardiologist, The Heart Group of LGHealth



INTRODUCTION

Atherosclerosis is driven by three main elements: the concentration of lipoproteins that contain Apolipoprotein B (Apo B), which adhere and diffuse into the vascular endothelium by mass gradient transfer; the loss of endothelial integrity (hypertension and reactive oxygen species); and a supra-physiologic inflammatory response.

For at-risk patients, aggressive statin treatment to goal lowers the incidence of cardiovascular events by 30%, but unfortunately these individuals are still exposed to 70% of their pretreatment risk.

In an effort to understand this so-called residual risk, additional components of blood lipids have been investigated and are now easily obtained in clinical practice. This report reviews the rationale for considering the use of these advanced markers as part of global cardiovascular risk reduction.

BASIC LIPID BIOLOGY

Cholesterol serves as a precursor for sterol hormones and bile salts, and is also required for synthesis of cellular membranes. Triglycerides provide energy for cellular metabolism and energy storage. This constant need to deliver lipids to peripheral tissues is satisfied by hepatic manufacture of very-low density lipoprotein (VLDL).

Under the influence of microsomal transfer protein, the liver combines triglyceride, phospholipids, apolipoproteins B and E, and cholesterol ester to produce the VLDL particle, comprised of 60% triglyceride and 12% cholesterol.

VLDL is the 'grandparent particle' of low-density lipoprotein (LDL-C). The newly minted VLDL particle is released from the liver and is acted upon by lipoprotein lipase (LPL), releasing its component parts for the body's needs. As a result of LPL hydrolysis, the VLDL particle becomes smaller and intermediate density lipoprotein (IDL) is formed. The fate of IDL is either uptake by the hepatic receptor (for bile salt excretion or recycling into another VLDL particle), or further hydrolysis into LDL.

Each molecule of LDL contains one molecule of Apo B. In the absence of insulin resistance or high triglycerides, the LDL particle contains 90% cholesterol ester and 10% triglyceride. It is the primary source of cholesterol used by the periphery for cellular membrane synthesis. If not used for this purpose, LDL is either taken up by the hepatic receptor or it adheres to the vascular endothelium and breaks through to the sub-endothelial space where it becomes oxidized and engulfed by macrophages resulting in the foam cell, the genesis of atherosclerosis. Notably, the hepatic receptor has less affinity for Apo B than Apo E (Apo E is lost during hydrolysis from IDL to LDL) and the result is greater circulation time compared to IDL.

This biology changes in the presence of insulin resistance or hypertriglyceridemia. Both these conditions activate the enzyme CETP (cholesterol ester transfer protein), which promotes the transfer of triglycerides from VLDL to IDL, LDL, and HDL in exchange for cholesterol. This activation of CETP is a double-edged sword that affects atherosclerosis in two ways:

On one hand, LDL—now laden with excess triglycerides—becomes an attractive target for hepatic lipase which aggressively hydrolyzes the particle and imparts such a change in conformation that the hepatic receptor fails to recognize it with the same affinity. This failure further extends the particle's already prolonged circulation time to several days, which increases the opportunity for it to be bound to endothelium and accelerate atherosclerosis. But since total LDL concentration does not change with this CETP-mediated alteration in chemistry, one might be lulled into a false sense of security that LDL may be at or close to goal.

The other edge of the sword involves the CETP mediated transfer of triglycerides to HDL. Similar to the situation with triglyceride-laden LDL-C, hydrolysis of the laden HDL particle creates a misshapen particle. This results in the loss of the anti-atherogenic particle apolipoprotein A-1 (Apo A-1) which breaks off and is ultimately lost by renal excretion. Apo A-1 is the mediator of reverse cholesterol transport which

serves to remove oxidized cholesterol from the sub-endothelial space; loss of this favorable effect also accelerates atherosclerosis.

To summarize the deleterious sequence of events in reverse: CETP drives an increase in LDL circulation time and loss of the athero-protective Apo A-1; hypertriglyceridemia and insulin resistance drive CETP activation; visceral adiposity, (afflicting two-thirds of the US population) drives insulin resistance and hypertriglyceridemia. Of note, alcohol suppresses CETP activity and is the likely explanation for the favorable effect on atherosclerosis when used in moderation.

WHAT CLINICAL AND BIOCHEMICAL CLUES SUGGEST INCREASED CETP ACTIVITY?

Visceral adiposity is invariably present when the waistline increases above 35 inches in women and 40 inches in men. Visceral adiposity differs from superficial adiposity as it is highly active metabolically; inflammatory cytokines are produced, triglycerides rise, and the host becomes insulin resistant. Measuring the patient's waistline is without cost, and when it exceeds the above-mentioned parameters it strongly suggests heightened CETP activity.

The presence of triglycerides over 200 and an HDL below 50 in women and 40 in men also suggests increased CETP activity.

COMPONENTS OF ADVANCED LIPID TESTING APOLIPOPROTEIN B

All atherogenic lipoproteins contain Apo B. Measurement of Apo B captures all of the potentially atherogenic lipoproteins and is superior to measurement of LDL for CV risk assessment. This is especially true in patients with metabolic syndrome who often have high triglycerides.

For many patients, a fairly good approximation of their Apo B level is contained within the standard lipid panel, because at LGH the panel includes a calculation and report of the non-HDL cholesterol level, which tends to rise and fall in parallel with the Apo B level. The National Cholesterol Education Program has published guidelines for optimal Non-HDL levels, and similar to LDL-C goals, vary with the degree of overall risk.¹

LDL PARTICLE NUMBER

The LDL particle number (LDL-P), like Apo B, reflects the concentration of atherogenic particles

available for attachment and diffusion into the sub-endothelial space. Particle number is also superior to LDL for estimating CV risk.² Data from the Framingham Offspring Study³ show good correlation between LDL particle number and LDL-C until triglycerides rise above 100, because the greater the triglycerides the more discordant the correlation between LDL-C and LDL-P. In many patients the LDL often appears close to goal yet the particle number can be markedly elevated as a result of CETP activity.

At the Preventive Cardiology and Lipid Apheresis Clinic, we target LDL-P as <1000 for our high risk patients.

LDL SUBFRACTIONS

LDL particles are heterogenous in size and density. Intuitively, smaller, denser LDL particles might diffuse more readily across the endothelial border into the subendothelial space. After reviewing available data, the National Lipid Association issued a consensus statement that they did not find adequate evidence to support the routine measurement of LDL (and HDL) subfractions in clinical practice.⁴

LIPOPROTEIN A

More commonly referred to as 'L-P little a,' abbreviated Lp(a), this is an LDL particle which has formed a disulfide bond with Lipoprotein a. This process is inherited in autosomal dominant fashion and is relevant only when LDL is elevated.⁵ This particle is both atherogenic and prothrombotic, as it has sequence homology to plasminogen and competes for its receptor, thereby promoting ongoing thrombosis rather than thrombolysis. If LDL-C is elevated, Lp(a) levels above 50 are associated with an increased incidence of vascular events.

Circulating levels are determined purely by genetics, and can be lowered by Niacin, estrogen, lipid apheresis, and new anti-cholesterol agents. Enthusiasm for the use of extended release niacin has been tempered by a recent report in which this drug lowered Lp(a) by 21% and also improved other lipid parameters, but there was no reduction in cardiovascular events.⁶

WHO SHOULD RECEIVE ADVANCED LIPID TESTING?

In 2011, an expert panel of the National Lipid Association was convened to address the role of advanced lipid testing.³ The panel noted that interest in new biomarkers is driven by three major factors:

- for those with metabolic syndrome and diabetes, there is significant residual risk even when statin therapy is used for both primary and secondary prevention;
- the overweight epidemic and the marked increase in the prevalence of obesity has resulted in more patients with metabolic syndrome with significant residual risk;
- the knowledge that LDL-C is less predictive in this group.

Advanced markers are utilized to improve risk assessment or to adjust therapy. The following reflects the expert consensus panel and reflects our practice at the LGHealth Preventive Cardiology and Apheresis Clinic:

APO B

Risk Assessment:

The routine measurement of Apo B in low risk patients (<5% 10 year CV event risk) is not recommended.

For those at intermediate risk (5-20% 10 year CV event risk), those with recurrent events or a family history of premature CVD, measuring Apo B “would enable the best possible management of modifiable factors for vascular risk.”

On-Treatment Management:

As with risk assessment, measurement of Apo B is not recommended for management of treatment in low risk patients. For those with intermediate risk, recurrent events, or a family history of premature CVD, measurement is considered ‘reasonable for many patients.’

LDL-P

Risk Assessment:

Given the large number of individuals in whom LDL-C does not accurately reflect CV risk (diabetics and those with metabolic syndrome), measuring LDL-P is ‘reasonable for many patients’ and the finding of discordantly elevated LDL-P should warrant consideration of LDL-lowering therapy. Also, it is reasonable to measure LDL-P in those at intermediate risk, those with a premature family history of CHD, and those with recurrent events.

On-Treatment Management:

In low risk individuals, measuring LDL-P is not recommended as it not likely change treatment.

To ensure that LDL has been adequately lowered, on-treatment measurement of LDL-P is felt reasonable in many patients at intermediate risk who are treated to their LDL and Non-HDL goal; in individuals with CHD or CHD risk-equivalent on therapy; and in those with recurrent events. If LDL-P is discordantly elevated, intensification of therapy should be considered.

The expert panel also felt it appropriate to consider measuring LDL-P to insure adequacy of therapy in selected patients with a family history of premature CHD.

LP(A)

Risk Assessment:

In low risk patients, measurement of Lp(a) is not recommended.

Lp(a) levels are additive to CHD risk, and it is therefore reasonable to measure its level in those with a premature family history of CHD, and in those with established CHD with recurrent events despite appropriate therapy.

In those with CHD or CHD risk equivalent, and in those at intermediate risk, measuring Lp(a) can be considered for selected patients.

On-treatment management:

There is insufficient evidence at this time to warrant the measurement of Lp(a) in those at low or intermediate risk.

Citing the fact that aggressive LDL-C reduction is helpful in patients with elevated Lp(a) and LDL-C, the expert panel recommended that on-treatment Lp(a) measurement may be considered in those with CHD and CHD risk equivalent, premature family history of CHD, or recurrent events despite treatment.

PRACTICAL LIPIDOLOGY

Our practice at the Preventive Cardiology and Apheresis clinic is to calculate the individual’s risk, typically with either the Framingham Risk Score⁷, or for women, the Reynolds Risk Score⁸ which incorporates measures of inflammation and considers family history. This latter metric was developed in an effort to address the Framingham Risk Score’s tendency to underestimate risk in women, and it proved more predictive when validated prospectively.

Once we understand the risk, we treat as best we can to goal, based on the National Cholesterol Education Program recommendations. Goals vary with risk so our treatment must be individualized.

It is important to remember that a triglyceride level greater than 500 mg/dl takes therapeutic priority over LDL-C. At this level, all of the available lipases are saturated and the risk of pancreatitis rises steeply.

Although we have been discussing advanced lipid testing, it is important to remember these basics during every patient encounter:

1. Calculate risk per NCEP ATP III guidelines
2. Treat to goal per NCEP ATP III guidelines
3. Treat triglycerides > 500 mg/dl before LDL
4. Never forget TLC (therapeutic lifestyle changes)
5. Look for residual risk in treated patients
6. Consider advanced lipid testing in those who struggle with excess weight or metabolic syndrome, are diabetic, or have a family history of premature CHD.

PHARMA, THE TOUGH LOVE TALK, AND CARDIAC REHABILITATION ... AN EDITORIAL CONCLUSION

Pharma clearly understands the economic benefit of direct marketing to patients, as evidenced by numerous multimedia advertisements. After practicing medicine for nearly 25 years, I believe this phenomenon has made our job more difficult.

First, the requirement to divulge side effects during the advertisements often produces 'pharmacophobes.' Every practitioner has encountered the not-infrequent

patient who recites side-effects before we finish discussing why expanded medical therapy might be appropriate for their condition. They tout the benefits of a 'natural approach' (I let them know snake venom is natural) pitched on television shows and web sites where potions can be purchased that treat almost any ailment—usually without any data from well-designed clinical trials.

Second, the intense marketing barrage provides the subliminal message that there is a pill or procedure for whatever ails us. Such reliance on techno-pharmacology often lulls the consumer into suboptimal self-care.

Many think the stent or CABG has 'fixed the problem' and their life can go on in the same manner. We are obligated to educate and empower our patients to optimal health. I inform these patients they have an incurable disease whose nature is to recur, I tell them poor lifestyle choices always beat our best pills and procedures in the long run. Dedicating one's self to an appropriate diet and a vigorous lifestyle with social connections often leads to graceful aging.

Advances in cardiovascular medicine often abort the MI and ready the patient for discharge in short order. I believe one of the reasons cardiac rehab has shown a mortality benefit is its reinforcement of the self-care message.

If we providers don't reinforce the reality that the foundation of the patient's care and survival is in their hands, they will think otherwise.

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Dr. Deron is a cardiologist with The Heart Group of LG Health. He is a Fellow of the American College of Cardiology, a Fellow in the Society of Cardiac Angiography and Intervention and a Diplomate of the American Board of Clinical Lipidology.

Scott Deron, DO, FACC, FSCAI
The Heart Group of Lancaster
217 Harrisburg Avenue, #200
Lancaster, PA 17603
717-544-8300
sderon@theheartgroup.com