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Clinical Utility of Low-Density Lipoprotein Particles and Apolipoprotein B in Patients with Cardiovascular Risk

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INTRODUCTION

The role of low-density lipoprotein (LDL) particles in the development of atherosclerosis and cardiovascular disease (CVD) is well known.[1,2] Historically, the cholesterol content of LDL—low-density lipoprotein cholesterol (LDL-C)—has been used to represent LDL quantity. Since elevated LDL-C levels are strongly associated with coronary heart disease (CHD) events and reductions in high LDL-C levels with LDL particle-lowering therapies, such as statins, significantly reduce CHD risk,[3] consecutive guidelines from the National Cholesterol Education Program (NCEP) have established LDL-C as the primary target of cholesterol treatment to reduce CHD risk.[3] The leading principle of the NCEP Adult Treatment Panel (ATP) III guidelines is the higher the patient's risk, the lower the LDL-C level needs to be to reduce that risk.[4]

However, data from several studies demonstrate a curvilinear relationship between LDL-C and CHD events: risk is strongly linked to LDL-C levels when LDL-C levels are high, but is more weakly linked to LDL-C levels when LDL-C levels are moderate to low.[4,5] Substantial variability in CHD risk has also been observed across a wide range of cholesterol values in prospective studies.[6,7] Furthermore, on-treatment LDL-C values are often weak predictors of CHD risk in intervention studies.[7-10] Thus, LDL-C levels are relatively insensitive risk markers when values are near treatment goal levels suggested by guidelines for patients at high risk (<100 mg/dL) or moderately high risk (<130 mg/dL).

The commercial availability of reliable methods for LDL particle number (LDL-P) measurement now makes it possible to examine potential clinical consequences of using LDL-C in CHD risk management. Apolipoprotein B-100 (apo B) is the major protein constituent of LDL particles, and each LDL, intermediate-density lipoprotein, and very low-density lipoprotein (VLDL) particle contains a single molecule of apo B. Even among

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patients with elevated triglycerides (TGs), with the exception of type III hyperlipoproteinemia, more than 90% of total plasma apo B is associated with LDL particles.[11,12] When automated, routine immunochemical methods are utilized, apo B values provide an accurate estimate of LDL-P concentration. Nuclear magnetic resonance (NMR) is another reliable commercially available methodology for the direct quantification of LDL-P.[13]

Due to biological variability in lipid metabolism and the effects of lipid-lowering therapies, the cholesterol content carried in LDL particles varies greatly among patients and in the same patient over time.[14-17] When measures of LDL-P quantity differ from LDL-C in terms of percentiles, apo B[18-27] or NMR-measured LDL-P[16,28-32] consistently demonstrate a significantly stronger association with CHD outcomes than LDL-C in prospective epidemiologic studies and better predict on-treatment residual risk in clinical trials.[8,10,33-36]

> Low-density lipoprotein cholesterol measurements often do not accurately reflect LDL-P due to variable amounts of cholesterol carried within LDL particles.

Given these data, recently published guidelines and consensus statements have addressed the debate about LDL measurement in risk assessment and therapy management. A panel of 30 international experts concluded that CVD risk is more directly related to the circulating atherogenic LDL-P quantity than to cholesterol content (LDL-C) and advocated using apo B as a therapeutic target in managing patients on lipid-lowering therapy.[7] Consequently, Canadian and European cholesterol guidelines recommend apo B as an alternative target to LDL-C in moderate and high-risk individuals.[37,38]

Several US organizations concur with their international counterparts. In a consensus statement, the American Diabetes Association and the American College of Cardiology recommend apo B, LDL-C, and non-high-density lipoprotein cholesterol (non-HDL-C) as therapeutic targets in patients with cardiometabolic risk.[39] The American Association of Clinical Endocrinologists issued similar recommendations.[40] The American Association for Clinical Chemistry Lipoproteins and Vascular Diseases Division Working Group on Best Practices, as well as the National Lipid Association, agree with the need to incorporate measures of LDL-P as a therapeutic goal and advocate using apo B or NMR LDL-P goals equivalent to those for LDL-C in terms of population percentiles.[41,42]

Correlation, concordance, and discordance among alternate LDL measures

Because medical management is centered on LDL measurement, analytical differences between cholesterol and particle measures of LDL quantity are clinically important. LDL-C measurements often do not accurately reflect LDL-P due to variable amounts of cholesterol carried within LDL particles—a phenomenon mainly caused by 2 processes[7,14,16,43-45]:

- People with elevated TGs frequently have smaller, more cholesterol-poor LDL particles, and individuals with smaller LDL particles require almost 70% more particles to carry the same amount of LDL-C than those with larger particles.[14,43]
- When TG levels are elevated, or LDL levels are decreased, cholesterol ester transfer protein-mediated exchange of TGs and cholesterol esters between various lipoproteins results in altered LDL particles that are partially depleted in core cholesterol and enriched in core TG.[14,16]

LDL-C and measures of LDL-P (apo B or NMR) are highly correlated (correlation coefficient, r = ~0.8), indicating an overall linear relationship between the 2 laboratory measures.[16,31,44] However, significant individual variation may still exist between highly correlated measures. The concepts of concordance and discordance address the variability of 1 laboratory measure at a defined value of the other. If at a defined level of 1 biomarker there is a similar value for the other, the 2 measures are said to be concordant. Conversely, if 1 biomarker is substantially higher or lower at a defined level of the other biomarker, the values are considered to be discordant.[46]

Studies have evaluated the prevalence and magnitude of concordance or discordance between LDL measures in various populations using specified population-equivalent cut points to define corresponding values of

each measure.[14,15,44,45,47-49] In these studies, discordance between LDL-C and LDL-P was present in up to 50% of participants. The prevalence of discordance is even greater among patients with diabetes or cardiometabolic risk, even when LDL-C is low (<100 mg/dL) or very low (<70 mg/dL).[15,45]

Clinically significant discordance also extends to patient populations on lipid-lowering therapies. In an analysis of 18 trials of patients treated with usual-dose statins, Sniderman[17] found that reductions in LDL-C and non-HDL-C were significantly greater than reductions in apo B and NMR LDL-P. These findings indicate many patients who achieve LDL-C and non-HDL-C target levels have not achieved correspondingly low apo B or LDL-P targets, thereby demonstrating cholesterol and particle measures are not equal markers of therapy efficacy. When LDL-C and LDL-P or apo B measures are concordant, they similarly inform about the amount of LDL present and it is not possible to detect a difference between either measure and cardiovascular risk. However, to determine the clinical value of a new measure with respect to cardiovascular outcomes associations, the new biomarker must be evaluated in cases of discordance.[50] If the new measure is more strongly related to cardiovascular outcomes than the current marker in the discordant setting, then it is considered a superior target for adjudicating individual risk and response to therapy.

Clinical outcomes associated with LDL-C, non-HDL-C, and LDL-P

Several studies support the superior nature of apo B or LDL-P in predicting cardiovascular events compared with cholesterol measures (LDL-C or non-HDL-C) when these measures are discordant.[16,44,51,52] The Quebec Cardiovascular Study found there were significantly more CHD events among individuals with discordantly high apo B and low LDL-C levels compared to patients with concordantly low levels of both measurements.[44] Findings from the Framingham Offspring Study and the Multi-Ethnic Study of Atherosclerosis (MESA) were similar: among individuals with concordant LDL-C and NMR LDL-P levels, incident CVD events were substantially greater in those with high versus low LDL-C.[16,52] Among discordant individuals, the high-risk group exhibited high LDL-P results and low LDL-C values, whereas the low-risk group had low LDL-P results and higher LDL-C values. These outcomes further underscore that CHD risk tracks with measures of LDL-P, not LDL-C, when these 2 measures are discordant.

Recent studies also offer insight into the relationship between CHD and non-HDL-C. Because patients with elevated TG levels have cardiovascular risk that appears to be incompletely accounted for by LDL-C, non-HDL-C was recommended in the NCEP ATP III guidelines as a secondary treatment target for patients with TG levels greater than 200 mg/dL.[3,4] The foundation for this recommendation is that TG-rich lipoproteins (VLDL and remnant lipoproteins) are also atherogenic, and the addition of VLDL cholesterol to LDL-C would represent total "atherogenic cholesterol" (non-HDL-C), thereby more completely accounting for the risk from all atherogenic particles. A similar claim has been made for apo B measurement because, as previously stated, apo B is the major protein constituent of VLDL and LDL particles.[4,6] Several studies comparing the association of CVD risk with non-HDL-C, apo B, and LDL-C have found LDL-C to be the weakest predictor, offering support to the apparent importance of measuring all atherogenic lipoproteins.[4,6,7]

Several studies support the superior nature of apo B or LDL-P in predicting cardiovascular events compared with cholesterol measures (LDL-C or non-HDL-C) when these measures are discordant.

However, if the inclusion of TG-rich lipoproteins was the main explanation for non-HDL-C having superior predictive power for CHD compared with LDL-C, a particle measure of all atherogenic particles (VLDL particle number [VLDL-P] + LDL-P) should also have a stronger association with cardiovascular events than LDL-P alone. In the Framingham Offspring Study, non-HDL-C was more strongly associated with CVD events than LDL-C in men and women, but was less predictive of CVD events than LDL-P.[16] Adding VLDL-P to LDL-P did not significantly strengthen CVD associations compared with LDL-P alone. Rather than benefiting from the inclusion of all apo B particles, non-HDL-C was felt to be more predictive of risk than LDL-C because

non-HDL-C tracked more closely with changes in LDL-P levels than LDL-C. Similar findings have been noted in other studies in which non-HDL-C was less discordant with apo B than with LDL-C.[17,44,48]

Mixed observations have been published regarding the strength of cardiovascular outcome associations between non-HDL-C and apo B in a variety of meta-analyses.[53-56] Sniderman et al[54] analyzed 12 studies and concluded non-HDL-C was superior to LDL-C in predicting cardiovascular risk and apo B was superior to non-HDL-C. A meta-analysis performed by the Emerging Risk Factor Collaboration found no differences among the 3 measurements in risk prediction.[55,57]Among statin-treated patients, Boekholdt et al[56] found non-HDL-C had the strongest association with cardiovascular risk compared with LDL-C and apo B. Robinson et al[53] concluded apo B improved CHD prediction when added to LDL-C and non-HDL-C, but did not improve stroke or overall CVD risk prediction. Across all lipid-lowering therapies, apo B did not improve CVD risk prediction over cholesterol measures.

> Apolipoprotein B was more accurate in identifying risk than non-HDL-C in discordant patients.

These meta-analyses failed to separate populations into concordant and discordant groups, which limits determination of whether LDL-C or LDL-P measures track more closely with outcomes in the discordant setting.[50] Discordance between non-HDL-C and LDL-P is not infrequent, occurring in 44% of MESA participants.[58] To address this issue, Sniderman et al[51] performed a discordance analysis of apo B and non-HDL-C as CHD risk markers, using data from blood samples on 21 465 patients enrolled in the INTERHEART study, a multi-national, case-control study of acute myocardial infarction. The analysis revealed that, compared with the concordant group, when population percentiles of apo B were higher than those of non-HDL-C, cardiovascular risk was increased 48%, whereas when non-HDL-C was higher than apo B, cardiovascular risk was reduced 28%. Therefore, apo B was more accurate in identifying risk than non-HDL-C in discordant patients.

Using LDL-P in clinical practice

Given the prevalence and magnitude of discordance among LDL-C, non-HDL-C, and LDL-P measures, coupled with the superior outcome prediction of apo B or NMR LDL-P vs LDL-C or non-HDL-C when discordance is present, recent expert panel recommendations and guidelines advocate using apo B[7,38-42] or NMR LDL-P[41,42] as a target of therapy. We suggest the following strategy to incorporate LDL-P into clinical practice and evaluate treatment options to meet recommended targets of therapy.[46]

1. Assess clinical risk

The updated NCEP ATP III guidelines advocate classifying patients into one of the following risk categories based on clinical characteristics[4]: very high risk, high risk, moderately high risk, moderate risk, and low risk, with the intent of assigning more aggressive LDL-C goals based on increasing risk.

This strategy is appropriate, and as suggested by the updated NCEP ATP III guidelines, clinicians should use clinical judgment in assigning the appropriate risk category, taking into account all available information beyond traditional risk factors to refine the patient's risk assessment.[3]

2. Establish therapy goals appropriate for the degree of assigned risk

The updated NCEP ATP III guidelines recommend the following LDL-C treatment goals[4]:

Moderately high-risk patients	<130 mg/dL
High-risk patients	<100 mg/dL
Very high-risk patients	<70 mg/dL (optional)

These goals were established without definitive trial data comparing outcomes in patients treated to these predetermined target levels.[5] As previously described, evidence demonstrates that low measures of LDL-P are a better indicator of low risk than correspondingly low LDL-C or non-HDL-C values.[7,16,39,41] **Table 1** presents suggested cholesterol and particle (LDL-P or measured apo B) targets based upon data from large population studies and expert recommendations.[14,16,41,46,52]

3. Prescribe therapeutic lifestyle changes and medications as indicated

After addressing secondary causes of dyslipoproteinemia (eg, hypothyroidism, diabetes mellitus, kidney

TABLE 1. Suggested cholesterol and particle number goals of therapy[59]

Risk Category	Cholesterol Targets (LDL-C and non-HDL-C)		LDL-P Targets (NMR LDL-P or measured apo B)	
	LDL-C (mg/dL)	**non-HDL-C (mg/dL)**	**NMR LDL-P (nmol/L)**	**Measured apo B (mg/dL)**
High	<100 (may consider <70 based on clinical judgment)	<130 (<100 if LDL-C target of <70 is selected)	<1000 (may consider <800 based on clinical judgment)	<80 (may consider <70 based on clinical judgment)
Moderate	<130 (may consider <100 based on clinical judgment)	<160 (<130 if LDL-C target of <100 is selected)	<1300 (may consider <1000 based on clinical judgment)	<100 (may consider <80 based on clinical judgment)
Low[a]	<160 (ideal <130)	<190 (ideal <160)	<1600 (ideal < 1300)	<120 (ideal <100)

Abbreviations: apo B, apolipoprotein B-100; non-HDL-C, non-high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; LDL-P, LDL particle number; NMR, nuclear magnetic resonance.

[a]Ideal values recommended based on CHD event rates in prospective trials.[14,16] Clinical judgment should be used in determining individual patient goals.

disease, medications), clinicians should prescribe therapeutic lifestyle changes and pharmacologic therapy as needed.[3] It is important to note that, due to changes in the cholesterol content of LDL particles during therapy, some treatments lower LDL-C more than they lower particle number (statins, statin combination with ezetimibe or bile acid sequestrants), while others lower particle number more than they lower LDL-C (niacin, fibrates, or statin combination with niacin or fibrates).[60]

For moderate- or high-risk individuals, we suggest the integration of LDL-P targets into clinical decision making, as shown in **Table 2**. If patients are near or at LDL-C and non-HDL-C goals, measure apo B or NMR LDL-P to determine if the patient still has elevated LDL-P. If the patient is above goal for LDL-P, consider treatments that will aid in lowering LDL-P further. These include intensified efforts at therapeutic lifestyle changes and/or combination lipid-lowering therapy. This is especially true in patients with elevated numbers of small LDL particles (eg, those with metabolic syndrome or type 2 diabetes), in which combination therapy may help decrease TG levels or raise HDL-C.

4. Assess therapy efficacy and modify treatment as needed[46]

Repeat LDL-P measurement after 3 months of therapy to evaluate response if therapeutic changes are made to lower elevated LDL-P. If the patient has achieved the LDL-P target appropriate for his/her CHD risk category, continue therapy and check LDL-P annually. If not, consider further adjustment in therapy and reassess at 3-month intervals as needed until the patient has achieved levels appropriate for his or her risk status.

CONCLUSIONS

The association between elevated LDL particles and CHD risk is well established; however, cholesterol measures are poor markers of LDL quantity for many individuals. Commonly encountered variability in the amount of cholesterol carried in LDL particles makes LDL-C and non-HDL-C frequently discordant with particle measures of LDL quantity (apo B and NMR LDL-P). When discordance is present, apo B and NMR LDL-P are superior predictors of prospective CHD risk than are LDL-C and non-HDL-C.

TABLE 2. Pharmacologic approach to achieving LDL-P and TG goals[59]

		LDL-P (measured apo B or NMR LDL-P)	
		At goal	Not at goal
LDL-C and non-HDL-C	Near or at goal	No further therapy[a]	**Statin therapy** (expected LDL-P decrease) Less potent statin (<35%) (eg, fluvastatin, lovastatin, pravastatin) More potent statin (35%-55%) (eg, atorvastatin, pitavastatin, rosuvastatin, simvastatin)
			Bile acid sequestrant therapy (expected LDL-P decrease) Colestipol, cholestyramine, colesevelam (15%-30%)
			Cholesterol absorption inhibitor therapy (expected LDL-P decrease) Ezetimibe (15%-25%)
			Combination therapies (expected LDL-P decrease) Statin + ezetimibe/bile acid sequestrants (50%-70%) Statin + niacin (50%-70%) Statin + ezetimibe/bile acid sequestrant + niacin (>60%)
TG	<500 mg/dL	May consider TG-lowering therapy based on clinical judgment	**LDL-lowering therapy (see above)**
	>500 mg/dL	TG-lowering therapy (expected TG decrease) 1. Niacin (20%-45%) 2. Fibrate[b] (20%-50%) 3. Omega-3 (Fish oil) (20%-45%)	**Priority 1** – LDL lowering **Priority 2** – TG lowering Consider additional therapy (expected LDL-P decrease) Niacin (5%-25%) Fibrate[b] (5%-20%) Omega-3 (Fish oil) DHA + EPA (Neutral to 3%-5%—not significant in multiple trials) EPA only (4%-15%)

Abbreviations: apo B, apolipoprotein B-100; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; non-HDL-C, non-high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; LDL-P, LDL particle number; NMR, nuclear magnetic resonance; TG, triglyceride.

[a]More aggressive therapy may be needed based on clinical judgment.

[b]Fenofibrate or fenofibric acid preferred over gemfibrozil for combination therapy due to increased risk of rhabdomyolysis from gemfibrozil.

Many organizations and expert panels have published recommendations for use of apo B (or NMR LDL-P) as a target of therapy to ensure that individual patients have achieved the degree of LDL lowering appropriate for their levels of CHD risk. Reliable and cost-effective measures of apo B and NMR LDL-P are now routinely available in many laboratories. We suggest here an approach to incorporating LDL-P into clinical practice for patients with moderate to high cardiovascular risk. ●

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