Beyond Low-Density Lipoprotein Cholesterol

Defining the Role of Low-Density Lipoprotein Heterogeneity in Coronary Artery Disease

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Recent clinical trials in patients with coronary artery disease (CAD) provide evidence that low-density lipoprotein cholesterol (LDL-C) levels should be lowered even further to prevent recurrent CAD. However, despite more aggressive interventions for lowering LDL-C levels, the majority of CAD events go undeterred, perhaps related to the fact that intervention was not started earlier in life or that LDL-C levels represent an incomplete picture of atherogenic potential. Nevertheless, LDL-C remains the contemporary standard as the primary goal for aggressive LDL reduction. If triglycerides are >200 mg/dl, the measurement of non–high-density lipoprotein cholesterol (HDL-C) is recommended. Measurement of apolipoprotein (apo)B has been shown in nearly all studies to outperform LDL-C and non–HDL-C as a predictor of CAD events and as an index of residual CAD risk. This is because apoB reflects the total number of atherogenic apoB-containing lipoproteins and is a superior predictor of the number of low-density lipoprotein particles (LDL-P). Estimates of LDL-P and size can also be made by nuclear magnetic resonance spectroscopy, density gradient ultracentrifugation, and gradient gel electrophoresis. Although a number of studies show that such estimates predict CAD, LDL-P, and size often accompany low HDL-C and high triglyceride levels, and therefore such additional lipoprotein testing has not been recommended for routine screening and follow-up. Because apoB is a superior predictor of LDL-P, we recommend that apoB and the apoB/apoA-I ratio be determined after measurement of LDL-C, non–HDL-C, and the ratio of total cholesterol/HDL-C to better predict CAD and assess efficacy of treatment. (J Am Coll Cardiol 2007;50:1735–41) © 2007 by the American College of Cardiology Foundation

Elevated low-density lipoprotein cholesterol (LDL-C) is a well-established independent risk factor for coronary artery disease (CAD). A number of primary and secondary trials have demonstrated that lowering of LDL-C decreases the incidence of CAD. These trials have been reviewed in detail elsewhere (1–4) and include treatment with a fat-modified diet and therapeutic agents such as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins), fibrates, niacin, and bile acid sequestrants. These studies, in aggregate, are the basis for the recommendations of the National Cholesterol Education Program (NCEP) that LDL-C be lowered to <100 mg/dl in patients with CAD or CAD risk equivalents, such as diabetes or peripheral arterial disease.

The HPS (Heart Protection Study) (5), the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) study (6), and the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study (7) all indicated a significant benefit to lowering LDL-C well below 100 mg/dl. The NCEP-Adult Treatment Panel (ATP) III guidelines were therefore amended in 2004 by adding an optional goal of LDL-C <70 mg/dl in patients with recent acute coronary syndromes or those otherwise felt to be at “very high risk” for adverse cardiovascular events (2). Subsequently, the TNT (Treating to New Targets) study (8), with atorvastatin 80 mg/day versus 10 mg/day, and ASTEROID (A Study to Evaluate the Effect of Rosuvastatin [40 mg/day] on Intravascular Ultrasound-Derived Coronary Atheroma Burden) (9) both supported the more aggressive treatment of LDL-C to <70 mg/dl.

O’Keefe et al. (3) proposed that the threshold for atherosclerotic progression may be at an LDL-C level of <70 mg/dl. Still, despite aggressive use of statins, the majority of CAD events are not prevented (1–8). In the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study, the use of atorvastatin 80 mg/day compared with simvastatin 20 mg/day did not result in a significant reduction in the primary outcome of major coronary events (10). This may be due to the fact that these studies were of relatively short duration and in older adults. The benefit is likely to be greater if intervention is started earlier in life and continued for a longer time period (11). The presence of traditional risk factors such as hypertension, diabetes, obesity, elevated triglycerides (TG), and low high-
density lipoprotein cholesterol (HDL-C) may also render the LDL-C intervention less effective. The influence of nontraditional risk factors such as small, dense LDL particles, elevated levels of high-sensitivity C-reactive protein (hs-CRP), lipoprotein (a) [Lp(a)], homocysteine, and unknown genetic and environmental risk factors on recurrent CAD events is not completely understood (1,2).

Another possible contributory factor is that LDL-C does not reflect the atherogenicity of all of the apolipoprotein (apo)B-containing lipoproteins nor does it necessarily represent the total number of low-density lipoprotein particles (LDL-P) or the distribution of size within those particles. This is particularly true if small, dense LDL-P is elevated, leading to an underestimate of LDL-P by LDL-C. Low HDL-C with a normal LDL-C is often accompanied by increased small, dense LDL-P (12). Patients with hyper-TG may also have increased small, dense LDL-P, placing them at higher CAD risk than those hyper-TG patients with a normal LDL-P (13). Here we review the epidemiologic and clinical evidence that determination of LDL-P supplements the LDL-C measurement and has both diagnostic and therapeutic implications.

**Biochemical Basis of LDL Heterogeneity**

Low-density lipoprotein is a heterogeneous group of particles that vary in their core content of cholesterol (12–14). A greater amount of cholesterol in LDL creates larger, more buoyant particles (sometimes referred to as LDL subclass A). A lower amount of cholesterol in LDL generates smaller, denser particles (sometimes referred to as LDL subclass B). Each LDL particle, regardless of its cholesterol content, has 1 molecule of apoB for each LDL molecule (13). For 2 patients with the same LDL-C, the one with a preponderance of small LDL particles will have a greater LDL-P, carry a significantly greater risk of CAD, and may therefore benefit from more aggressive therapy (12–16).

**VLDL–IDL–LDL pathway.** Alterations in the very-low-density lipoprotein (VLDL)–intermediate-density lipoprotein (IDL)–LDL pathway, whether owing to genetic mutations, acquired disorders, diet, or other factors, result in variation in particle composition, size, and abundance (12–16) (Fig. 1). For example, the metabolic syndrome, diabetes, familial combined hyperlipidemia, and hyperapobetalipoproteinemia (hyper-apoB) are conditions in which increased synthesis and secretion of VLDL leads to the overproduction of small, dense LDL and HDL particles, a combination that increases cardiovascular risk (13–17) (Fig. 1). Insulin resistance or a defect in the normal activity of the acylation stimulatory protein can cause higher plasma free fatty acid levels, leading to greater hepatic free fatty acid uptake, increased TG production, decreased hydrolysis of apoB, and increased production and secretion of larger TG-rich VLDL particles (13–17) (Fig. 1).

An increased exchange of TG from VLDL for cholesteryl ester (CE) in LDL and HDL occurs via the CE transfer protein, resulting in cholesterol-depleted TG-enriched l-
poproteins that are subsequently converted into smaller, denser particles by hepatic lipase (Fig. 1). The TG-enriched LDL is hydrolyzed, leading to increased small, dense LDL-P (15). The TG-rich HDL is also modified by hepatic lipase, producing smaller HDL that is cleared more rapidly by the kidneys, contributing to lower levels of HDL-C and its major apolipoprotein, apoA-I (Fig. 1). Such abnormalities in the VLDL–IDL–LDL pathway are often manifested by the dyslipidemic triad of hyper-TG, increased small, dense LDL-P, and low HDL-C.

The Contemporary Standards: LDL-C and Non–HDL-C

LDL-C. Aggressive reduction of LDL-C is the current primary goal of lipid-lowering therapy (1–10). The LDL-C reflects the cholesterol content of several atherogenic lipoproteins, including LDL, IDL, and Lp(a). The conventional lipid panel measures levels of total cholesterol (TC), HDL-C, and TG and calculates LDL-C using the Friedewald equation (18). To use this formula, the patient must be fasting with a TG level <400 mg/dl. As LDL-C nears goal, the inaccuracies of the Friedewald equation are amplified (19). For example, calculated LDL-C generally underestimates the true concentration of small, dense LDL particles, especially when the TG level is >200 mg/dl (13). Given these limitations of LDL-C, the NCEP recommended using non–HDL-C (total cholesterol – HDL-C) as a secondary target of therapy when the TG level is >200 mg/dl (1).

Non–HDL-C. The non–HDL-C estimates the cholesterol concentration of all the apoB-containing lipoproteins, namely VLDL, IDL, LDL, and Lp(a), in contrast to LDL-C, which does not include VLDL-C. The non–HDL-C can be measured nonfasting. If the TG level is elevated to >200 mg/dl, the non–HDL level will reflect the increase in VLDL-C. The non–HDL-C appears superior to LDL-C estimation in establishing CAD risk and monitoring treatment (20–23). However, lipid levels do not necessarily equate to lipoprotein particle levels, and non–HDL-C does not permit a determination of whether there is also an increase in small, dense LDL-P in the hyper-TG patient.

Beyond LDL-C and Non–HDL-C

ApoB measurement. The apoB level reflects the total number of atherogenic apoB-containing lipoproteins, because each chylomicron, chylomicron remnant, VLDL, IDL, LDL, and Lp(a) particle contains 1 molecule of apoB. However, 90% of total plasma apoB is contained within the LDL particles (13). Thus, for a given LDL-C level, a higher apoB level indicates higher LDL-P. Measurement of apoB (as well as apoA-I) does not need to be done in the fasting state, has been standardized by the World Health Organization, and is available in most large commercial laboratories (24).

Moreover, apoB has been shown in nearly all studies to outperform LDL-C and non–HDL-C measurements in cardiovascular risk stratification (25–30). These include several large, prospective studies such as AMORIS (Apolipoprotein-Related Mortality Risk Study) (29), the Health Professionals Follow-Up Study (27), the Quebec Cardiovascular Study (25,26), and the study by Moss et al. (30).

Benn et al. (31) recently reported that apoB had a higher predictive ability than LDL-C for ischemic cardiovascular disease in 9,231 asymptomatic Danish men and women. Using receiver-operating characteristic curves, they found that the predictive ability of non–HDL-C was similar to apoB. However, the interindividual biological variation for apoB (coefficient of variation [CV] 6.9%) was superior to non–HDL-C (TC CV 6% plus HDL-C CV 7.1%), indicating that repeated measurements of apoB are more reliable in a single patient. Apolipoprotein B also appears to be a better predictor of subsequent CAD events in patients on treatment with statins (28,32).

Ratio of apoB to apoA-I. Results from a number of epidemiologic studies indicated that the ratio of apoB to apoA-I was the strongest predictor of CAD (28). In both the placebo and the treatment groups from the AFCAPS/TEXCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) trial, the apoB/apoA-I ratio was a robust predictor of CAD (32). Similarly, van Lennep et al. (33) reported in patients with CAD on statin therapy that only apoB and the apoB/apoA-I ratio predicted myocardial infarction and all-cause mortality, whereas LDL-C and TG did not. In both men and women from the AMORIS (Apolipoprotein-Related Mortality Risk Study) study, the superiority of the ratio of apoB to apoA-I, compared with the TC/HDL-C ratio, became more obvious as risk of CAD increased (28). In men, the relative risk of CAD increased at an apoB/apoA-I ratio of 1.0, and the comparative figure for females was 0.86 (28). These results in aggregate are not surprising, given that increased LDL-P is usually accompanied by low HDL and apoA-I (Fig. 1).

The percentile distributions for LDL-C, non–HDL-C, and apoB are available from the Framingham Heart Study (23,34,35) (Table 1). For a particular goal for LDL-C, measurement of apoB and the apoB/apoA-I ratio predicted myocardi infarction and all-cause mortality, whereas LDL-C and TG did not. In both men and women from the AMORIS (Apolipoprotein-Related Mortality Risk Study) study, the superiority of the ratio of apoB to apoA-I, compared with the TC/HDL-C ratio, became more obvious as risk of CAD increased (28). In men, the relative risk of CAD increased at an apoB/apoA-I ratio of 1.0, and the comparative figure for females was 0.86 (28). These results in aggregate are not surprising, given that increased LDL-P is usually accompanied by low HDL and apoA-I (Fig. 1).

Table 1. Estimated Percentiles of LDL-C, Non–HDL-C, ApoB, and LDL-P

<table>
<thead>
<tr>
<th>Percentile</th>
<th>LDL-C (mg/dl)</th>
<th>Non–HDL-C (mg/dl)</th>
<th>ApoB (mg/dl)</th>
<th>LDL-P (nmol/l)</th>
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<tr>
<td>5th</td>
<td>80</td>
<td>110</td>
<td>70</td>
<td>800</td>
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<tr>
<td>10th</td>
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<td>120</td>
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<td>900</td>
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<td>95th</td>
<td>200</td>
<td>230</td>
<td>150</td>
<td>2,100</td>
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</table>

Estimates were derived from the Framingham Heart Study (23,34,35). Men and women were combined.

ApoB = apolipoprotein B; LDL-C = low-density lipoprotein cholesterol; LDL-P = total number of low-density lipoprotein particles; non–HDL-C = total cholesterol – high-density lipoprotein cholesterol.
apoA-I in men and women from the Framingham Heart Study (35) are also provided in Table 2. We propose that in addition to apoB, the ratio of apoB/apoA-I be included as alternative goals in consensus recommendations for LDL reduction and HDL increase.

Other assessments of LDL particle number and size. The LDL-P is determined by the rate at which the LDL particles are produced and cleared from the circulation (13–16) (Figs. 1 and 2). Furthermore, there are documented variations between different ages, genders, and races (36–38). For a given LDL-C level, an increase in small, dense LDL-P is associated with increased atherogenesis, which may explain some of the variation in risk between different individuals and populations (36–38). More direct measures of LDL-P may help to further delineate the risk of CAD attributable to metabolic abnormalities such as diabetes and the metabolic syndrome (14,16,17).

The LDL-P appears to be a particularly strong predictor of CAD in women. In the prospective CHS (Cardiovascular Health Study) (37), NMR-determined LDL-P and small LDL particle size predicted incident CAD, primarily among elderly women. The LDL-P remained significant, even after adjustment for traditional risk factors, whereas LDL particle size did not. Mackey et al. (40) found that LDL-P, small, dense LDL, and large VLDL were positively associated with coronary artery calcification in healthy postmenopausal women, after adjustment for age, systolic blood pressure, current smoking, LDL-C, HDL-C, and TG. Blake et al. (15) found that LDL-P in healthy women was independently predictive of future myocardial infarction, even after adjustment for the ratio of TC to LDL-C, apoB, and hs-CRP.

Rosenson et al. (41) measured LDL and HDL particle size and concentration by NMR spectroscopy in frozen plasma samples of placebo- and pravastatin-treated subjects. Whereas lipid levels did not predict angiographic progression of CAD, LDL-P strongly correlated with progression (41).

In the MESA (Multiethnic Study of Atherosclerosis) study, Mora et al. (42) studied the association of LDL-P and particle size by NMR with carotid intima-media thickness (IMT) in over 5,000 apparently healthy individuals. When controlling for traditional CAD risk factors and LDL subclass correlation, both large and small LDL-P, but not LDL size, were significantly associated with carotid IMT.

Table 2

<table>
<thead>
<tr>
<th>Percentile</th>
<th>5th</th>
<th>10th</th>
<th>25th</th>
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<th>75th</th>
<th>90th</th>
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<td>31</td>
<td>37</td>
<td>43</td>
<td>51</td>
<td>61</td>
<td>67</td>
</tr>
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<td>39</td>
<td>46</td>
<td>55</td>
<td>66</td>
<td>77</td>
<td>84</td>
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<tr>
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<td>116</td>
<td>132</td>
<td>154</td>
<td>181</td>
<td>206</td>
<td>224</td>
</tr>
</tbody>
</table>

Estimates were derived from the Framingham Heart Study (35).

 apoA-I = apolipoprotein A-I; HDL-C = high-density lipoprotein cholesterol.

Nuclear magnetic resonance (NMR) spectroscopy rapidly determines the sizes and concentrations of 15 lipoprotein subclasses based on the spectral characteristics of methyl groups within the lipid molecules and the difference in size of the lipoprotein particles (12). The LDL-P by NMR includes IDL and 3 LDL subclasses. Nuclear magnetic resonance has been validated against existing methods of lipoprotein subclass determination (12); however, there is no international standardization program. Nuclear magnetic resonance was only performed by LipoScience (Raleigh, North Carolina).

The LDL-P appears to be a particularly strong predictor of CAD in women. In the prospective CHS (Cardiovascular Health Study) (37), NMR-determined LDL-P and small LDL particle size predicted incident CAD, primarily among elderly women. The LDL-P remained significant, even after adjustment for traditional risk factors, whereas LDL particle size did not. Mackey et al. (40) found that LDL-P, small, dense LDL, and large VLDL were positively associated with coronary artery calcification in healthy postmenopausal women, after adjustment for age, systolic blood pressure, current smoking, LDL-C, HDL-C, and TG. Blake et al. (15) found that LDL-P in healthy women was independently predictive of future myocardial infarction, even after adjustment for the ratio of TC to LDL-C, apoB, and hs-CRP.

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In the prospective EPIC (European Prospective Investigation Into Cancer and Nutrition)-Norfolk study (22) in 25,663 subjects, both LDL-P, as assessed by NMR, and non–HDL-C were more closely associated with CAD than LDL-C. After HDL-C and TG levels were accounted for, LDL-P lost its discriminative power over LDL-C. Consistent with the MESA study, the EPIC-Norfolk study also found that LDL size was not predictive of CAD after adjustment for LDL-P. These results argue against the routine implementation of determining LDL-P number and size by NMR for CAD risk assessment. However, the fact that patients with low HDL-C and/or higher TG often have elevated numbers of LDL-P, without having high LDL-C, may enable their LDL-related CAD risk to be managed more effectively. Although data from clinical intervention studies (see subsequent text) support LDL-P by NMR as an alternative treatment target (but not superior to apoB), the value of LDL-P monitoring as an additional treatment target beyond LDL-C needs to be assessed in intervention trials.

**DGU.** In DGU, lipoprotein fractions from a density gradient are eluted systematically and the cholesterol content determined. The method allows an estimate of the relative distribution of cholesterol but not particle number within the IDL and LDL subclasses. Evidence from several angiographic trials using DGU indicated that treatment benefit is reflected in the conventional lipid profile, calculated LDL-C often does not reflect small, dense LDL-P in such patients (13). Recognition of this important, because increased small, dense LDL-P due to enhanced production of TG-rich VLDL appears to be the single most frequent dyslipidemia in patients with premature CAD (13–16). Thus, a low or normal LDL-C level may result in a less aggressive approach than may be clinically indicated, particularly in the patient who may benefit more from combined lipid-altering therapy.

Multiple biochemical and cellular mechanisms of atherogenic small, dense LDL particles have been proposed (16) (Fig. 2). It is still incompletely resolved whether risk of CAD is simply related to LDL-P per se, or whether LDL size is also an independent predictor of CAD (see preceding text). Although studies have demonstrated improvement in LDL particle size distribution with pharmacologic intervention, it remains to be established whether risk stratification based on LDL size by “advanced” or additional lipoprotein testing is sufficiently additive to merit a change in management strategies.

### Altering LDL Particle Number and Size

Statins are the most potent class of drugs to reduce LDL-P, including small, dense LDL-P. Higher doses of the more powerful statins may also decrease VLDL production, leading to a small shift from small, dense to larger LDL particles. Both niacin and fibrates convert small, dense LDL into larger, more buoyant LDL.

Although LDL-P clearly predicts CAD events, it is unclear if altering LDL size decreases CAD events independent of any effect on lowering LDL-P. In the VA-HIT (Veterans Affairs High-Density Lipoprotein Intervention Trial) study (50) subjects with low HDL-C and average LDL-C treated with gemfibrozil had a significant decrease in CAD events compared with placebo, an effect proportional to the increase in HDL-C, because LDL-C was not decreased with gemfibrozil. Using NMR, Otvos et al. (51) reported that gemfibrozil lowered small, dense LDL-P, thereby increasing total LDL size. Total HDL-P, particularly HDL-3, increased with gemfibrozil. These changes in particle composition independently decreased risk of new CAD events and explained a significant amount of the benefit of gemfibrozil in the VA-HIT study.

Additionally, the DAIS (Diabetes Atherosclerosis Intervention Study) trial (52) showed that patients with type 2 diabetes treated with fenofibrate had a significantly decreased rate of angiographic CAD progression and a greater increase in LDL size compared with placebo controls. In a substudy, Vakkilainen et al. (53) found that small LDL size was associated with greater CAD progression, regardless of treatment group, and that fenofibrate produced a greater increase in LDL particle size compared with placebo. In contrast, the FIELD (Feno-
fibrate Intervention and Event Lowering in Diabetes) study (54) was associated with a nonsignificant 11% reduction in the primary end point (coronary heart disease death and non-fatal myocardial infarction); however, changes in LDL-P and LDL particle size were not reported.

**Perspectives and Future Directions**

The evidence supporting the incremental value of measuring apoB is strong and internally consistent. The Thirty-Person/Ten-Country Panel has proposed that evidenced-based guidelines endorse alternatives such as apoB in both men and women (28), a recommendation further supported by the results of the large Copenhagen City Heart Study (31). Statin-treated patients may have a proportionally higher apoB than LDL-C, indicating that too many LDL-P are still present. Those patients will require further intervention, often in the form of combined lipid-altering drugs. For patients with CAD, CAD risk equivalents, or a high risk of CAD, a more aggressive LDL-C goal of <70 mg/dl should be considered. This goal is in fact less than the fifth percentile for LDL-C. The recently proposed goal of <80 mg/dl for apoB in such high-risk patients is about the 25th percentile. Although it is not certain what the equivalent goal of apoB should be when the LDL-C goal is <70 mg/dl, the equivalent percentile for apoB is <60 mg/dl.

Recent evidence indicates that non–HDL-C and LDL-P also provide additional prognostic information over LDL-C. Population-based percentiles for LDL-C, non-HDL-C, apoB, and LDL-P are available from the Framingham Heart Study (36). Alternative goals for LDL-P as well as apoB related to current NCEP treatment goals for LDL-C and non–HDL-C should be considered in future recommendations.

Further study is needed to define the incremental value of LDL-P and LDL size in the setting of LDL-C targets <70 mg/dl. The preponderance of small, dense LDL-P may provide independent information that predicts risk beyond the traditional lipid profile, particularly in the presence of the dyslipidemic triad. With regard to high LDL-P and low HDL-C, there is evidence that the ratio of apoB/apoA-I may be the strongest predictor of CAD and that such measurement could be incorporated into clinical practice. Population-based percentiles for men and women for apoA-I and HDL-C also are available from the Framingham Heart Study (36).

Only through well-designed prospective clinical trials will we be able to determine when lipoprotein heterogeneity analysis is justified and how best to use the information. For now, selective measurement of apoB might be incorporated into clinical practice (when the TG level is above normal), with the addition of the apoB/apoA-I ratio and LDL-P only when it is likely to change clinical management.

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