Is It LDL Particle Size or Number that Correlates with Risk for Cardiovascular Disease?

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The role of low-density lipoprotein cholesterol (LDL-C) in the pathogenesis of cardiovascular disease (CVD) and the clinical benefit of lowering LDL-C in high-risk patients is well established. What remains controversial is whether we are using the best measure(s) of LDL characteristics to identify all individuals who are at CVD risk or if they would benefit from specific therapies. Despite the successful LDL-C reduction trials, substantial numbers of patients continue to have clinical events in the treatment groups. The size of LDL particles and assessment of the number of LDL particles (LDL-Num) have been suggested as a more reliable method of atherogenicity. Each LDL particle has one apoprotein B-100 measure attached; therefore, determination of whole plasma apoprotein B can be considered the best measure of LDL-Num. Because the cholesterol content per LDL particle exhibits large interindividual variation, the information provided by LDL-C and LDL-Num is not equivalent. Individuals with the same level of LDL-C may have higher or lower numbers of LDL particles and, as a result, may differ in terms of absolute CVD risk. LDL particle size and number provide independent measures of atherogenicity and are strong predictors of CVD.

Introduction

Within the past two decades, clinical trials of low-density lipoprotein cholesterol (LDL-C) reduction have demonstrated that LDL-C reduction in primary and secondary prevention trials can reduce the relative risk of clinical cardiac events approximately 25% [1]. Arteriographic investigations have demonstrated that LDL-C reduction can reduce the rate of arteriographically defined disease progression [2–5]. Despite the relative success of LDL-C reduction, close examination of the trial results reveals that a substantial number of patients who received treatment and achieved significant LDL-C reduction still had a clinical event or evidence of arteriographic progression [1]. Studies assessing LDL subclass distribution have shown increased rates of arteriographic progression associated with small LDL [6,7]. In arteriographic treatment studies, change in small, dense LDL has been reported to be the most powerful predictor of arteriographic change [8,9].

The importance of lipoprotein subclasses is not a recent revelation. In the late 1950s, Dr. John Gofman and colleagues at the Donner Laboratory (University of California) investigated the relationship of lipoprotein subclasses to atherosclerosis in the Framingham and Lawrence Radiation Laboratory at Livermore studies [10]. Their contribution included the association of multiple lipoprotein subclasses defined by Svedberg flotation intervals, assessed in the analytic ultracentrifuge. Since then, a substantial body of knowledge has become available regarding specific biochemical and metabolic features of the intermediate-density lipoprotein (IDL), LDL, and high-density lipoprotein (HDL) subpopulations that relate to atherogenesis [11]. In the past 50 years, investigators have extended the work of Gofman and colleagues to involve a plethora of investigations that assessed the physiologic role of lipoprotein subclasses within the entire subclass distribution and their relationship to atherosclerosis [12]. These investigations bridged the gap between basic science and clinical research and recently have included genetics and arteriographic trials [13–15]. This is of particular clinical importance because clinical trials utilizing combination therapy that has a beneficial effect on LDL subclass distribution have been shown to be greatly superior to LDL-C lowering alone in regard to clinical events, arteriographic benefit, and mortality [16,17••].

In this article, we review the clinical trials investigating the associations of cardiovascular risk with LDL subclass distribution and LDL particle number (LDL-Num). We conclude that both LDL particle size (quality) and particle number (quantity) each have a powerful relationship to

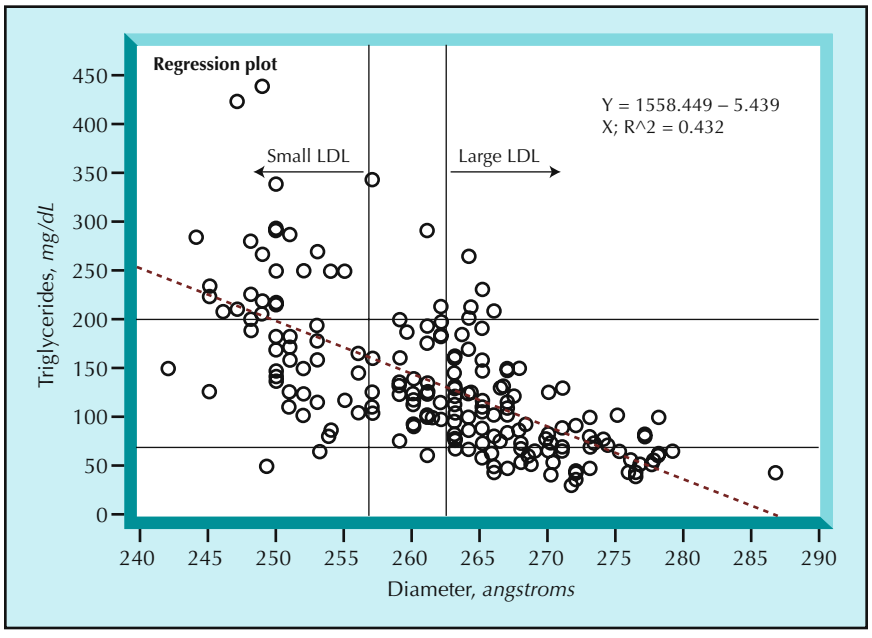

Figure 1. Correlation of fasting triglycerides (TGs) and low-density lipoprotein (LDL) diameter in 180 patients participating in a nicotinic acid investigation ($r = 0.66$; $P < 0.0001$). Patients with LDL particle diameter of 257 angstroms or less are classified as LDL pattern B, and those with LDL particle diameter greater than 262 angstroms are classified as LDL pattern A. Although most patients with fasting TGs greater than 200 mg/dL are likely to exhibit small LDL pattern B, and those with fasting TGs less than 70 mg/dL are likely to exhibit LDL pattern A, the overlap in LDL subclass pattern when fasting TGs are between 70 and 200 mg/dL makes the use of this relationship hazardous in regard to accuracy of LDL subclass pattern determination in individual patients. (*Data from* Superko et al. [16].)

coronary heart disease (CHD) risk, and the combination of both laboratory disorders reflects even higher CHD risk.

LDL Heterogeneity and Lipoprotein Subclasses

Lipoproteins comprise a heterogeneous and polydisperse population of particles, with sizes from the large triglyceride (TG)-enriched chylomicrons, very low-density lipoproteins (VLDL), and the dense and small protein-rich HDL particles. Classically, LDL particles are defined in terms of hydrated density as the fraction with density between 1.006 and 1.063 kg/L as obtained by preparative ultracentrifugation. This so-called broad-cut LDL fraction is heterogeneous, containing several different lipoproteins: intermediate-density lipoprotein (IDL), with a hydrated density of 1.006 to 1.019 kg/L and that includes chylomicrons and VLDL remnants; the main LDL region, with a hydrated density of 1.019–1.063 kg/L; and lipoprotein(a) (Lp(a)). Lp(a) is an LDL-like particle on which apoprotein (apo) a is connected by one or more disulfide bonds to apoB-100 [18]. On an agarose gel at pH 8.6, most LDL particles migrate to the β region and may be termed β lipoproteins. Lp(a) comigrates to the pre-β region together with VLDL, whereas IDL forms a broad band between β and pre-β. In clinical practice, LDL-C is commonly determined by a method that involves precipitation of apoB-containing particles and subsequent calculation of LDL-C based on the assumption that VLDL-C is equal to TGs [19]. LDL-C values obtained by this method may contain IDL particles [20]. In practice, the fractions separated by electrophoresis, chemical precipitation, and chromatography are often simply referred to as LDL, although they do not exactly correspond to those by ultracentrifugation. Thus, LDL particles are defined operationally in terms of the analytical procedure used to isolate them and include a family of similar particles that vary in size and composition [21]. The heterogeneity of LDL extends beyond IDL and Lp(a) with several different subparticle classes. Proposed nomenclatures for the subclasses are based on density or size, determined by ultracentrifugation or polyacrylamide gradient gel electrophoresis (GGE) [11].

Human plasma LDLs include multiple distinct subclasses of different particle size that can be identified by nondenaturing polyacrylamide GGE [22]. Utilizing this method, seven distinct LDL subclasses have been identified based on their diameter: LDL-I (27.2–28.5 nm), LDL-IIa (26.5–27.2 nm), LDL-IIb (25.6–26.5 nm), LDL-IIIa (24.7–25.6 nm), LDL-IIIb (24.2–24.7 nm), LDL-IVa (23.3–24.2 nm), and LDL-IVb (22.0–23.3 nm) [22,23]. Several case-control, nested case-control, and prospective studies have revealed that a predominance of smaller LDL particles (ie, LDL-III or LDL-IV) is associated with increased CHD risk [3,24–28]. LDL size assessment is most commonly determined by GGE, and assignment of LDL subclass phenotypes is based on the peak particle diameter of the major LDL peak. GGE analysis frequently reveals two or more LDL peaks representing two or more LDL subclasses based on mean peak particle diameter measured in angstroms (Å). On GGE analysis, LDL phenotype A (larger, more buoyant LDL) is defined as an LDL subclass pattern with the major peak at a particle diameter of 262 Å or greater, whereas the major peak of LDL phenotype B (small, dense LDL) is at a particle diameter of 257 Å or less. LDL phenotype AB (or intermediate) is defined with the major peak at a particle diameter between 258 and 262 Å. In most healthy people, the major subspecies are large or buoyant (pattern A), whereas the smaller, denser LDL (pattern B) subspecies are generally present in small amounts [23].

LDL-Num is determined by LDL apoB concentration and can be estimated by nuclear magnetic resonance (NMR), based on a correlation with apoB concentration [29].

In general, the higher the TG value the smaller the LDL size, and the lower the HDL-C level the smaller the LDL size. However, this relationship is most useful clinically when TGs are in excess of 200 mg/dL or less than 70 mg/dL (Fig. 1). Associated with the LDL pattern B phenotype and an abundance of small LDL are reduced levels of the protective HDL2 subclass [30]. This inverse relationship results in elevated levels of the atherogenic LDL subclass and low levels of the protective HDL2 subclass and creates an atherogenic milieu that increases CHD risk threefold [13,24,25,28,31]. Thus, the relative atherogenic contribution of small LDL or low HDL2 is difficult to separate, and independent contribution to CHD risk is not to be expected due to the inverse physiologic relationship.

Laboratory Considerations

Laboratory methods of LDL subclass distribution determination are not standardized, and caution is advised in regard to the accuracy and reproducibility of commercial laboratory methods. The gold standard laboratory method of determining lipoprotein subclass distribution is based on density as determined by analytic ultracentrifugation (ANUC) [10]. This method employs a highly accurate and reproducible ultracentrifugation method that characterizes LDL subclasses by flotation intervals into 12 regions. The ANUC method is time consuming, expensive, and available only in a limited number of research laboratories. Nondenaturing GGE was developed as a less expensive method of determining lipoprotein subclass distribution on the basis of their differing sizes and, at the University of California–Berkeley, run in parallel with ANUC in multiple investigations [22]. Important to the accuracy of this technique is the method and quality control of gel production. A rapid ultracentrifugation method, termed vertical auto profile, has been used to determine relative flotation index as a determination of change in LDL buoyancy [32]. This method determines the cholesterol concentration of multiple lipoprotein fractions based on density. During profile decomposition, peak heights for predefined subcurves for subclasses are simultaneously determined until the sum of the squared deviations between the sum of the subcurves and the parent profile is minimized using linear regression. A relatively new method used to estimate lipoprotein subclass distribution is NMR [33]. NMR signals are derived from methyl groups on phospholipids, cholesterol, cholesterol ester, and TGs. NMR assumes a constancy of lipid mass contained within a particle of given diameter and phospholipid composition, and thus methyl lipid NMR signal. This system uses a library of reference spectra of lipoprotein subclasses incorporated into a linear least-square fitting computer program that works backward from the shape of the composite plasma methyl signal to calculate the subclass signal intensities [33]. Microfluidic gel electrophoresis is the most recent method developed to separate lipoprotein subclasses and utilizes the characteristics of gel electrophoresis on chip technology to obtain separations standardized to ultracentrifugation [34•]. National standardization programs do not monitor the accuracy of lipoprotein subclass determination by any of these methods.

LDL-Num is defined as the LDL apoB number because each LDL particle has one and only one apoB attached. Two major apoprotein B types are common and include the hepatically derived apoB-100, which is attached to LDL particles, and apoB-48, which is derived from the intestines and primarily attached to TG-rich lipoprotein particles and not LDL particles [35]. Thus, the quintessential measure of LDL-Num is LDL apoB or apoB-100 determination. NMR-derived particle number has some correlation with particle number but is a calculated value.

Small, Dense LDL, Atherogenic Lipoprotein Profile, and Metabolic Syndrome

Small, dense LDL has several characteristics that are linked to atherogenesis: long residence time in plasma, enhanced susceptibility to oxidation, arterial proteoglycan binding, and permeability through the endothelial barrier [11,31]. Together, these findings have led to the hypothesis that small, dense LDL is a potent atherogenic lipoprotein and a true determination of its value can be used to improve CHD risk prediction and evaluate response to lipid therapy [36]. Furthermore, small, dense LDL is often part of a group of high-risk characteristics, including elevated TGs, low HDL, low HDL2, diabetes, insulin resistance, obesity, and metabolic syndrome [37]. This has led logically to the concept that it contributes to the high rate of CHD in these groups, and prior to the popularization of the term *metabolic syndrome* it was termed the *atherogenic lipoprotein profile* [37]. The statistical association between small, dense LDL and these other high-risk conditions challenges proponents of the hypothesis to show a direct, independent relationship between small, dense LDL and CHD risk [38]. However, due to the intertwined physiologic relationships, statistical independence should not be expected.

LDL Particle Size and Cardiovascular Risk

Although increased plasma LDL-C concentration is considered one of the most important risk factors for CHD, many individuals in whom CHD develops have LDL-C levels in the same range as individuals who do not develop CHD. This observation challenges the traditional approach of using LDL-C concentrations as the main lipid target in the management of CHD risk [39]. A predominance of small, dense LDL has been accepted as an emerging cardiovascular risk factor by the National Cholesterol Education

Program Adult Treatment Panel III [40]. LDL size seems to be an important predictor of cardiovascular events and progression of CHD. Evidence suggests that both quality (particularly small, dense LDL) and quantity (particle number) may increase cardiovascular risk. In multivariate analysis of large clinical trials, it has been shown that LDL peak particle diameter is statistically independent of traditional risk factors such as fasting TGs, LDL-C, HDL-C, and body mass index [41]. However, other authors have suggested that LDL size measurement does not add information beyond that obtained by measuring LDL concentration, TG levels, and HDL concentrations in regard to CHD risk prediction [42••].

The pathophysiologic rationale for the role of small, dense LDL in the atherogenic process is based on several factors. First, in a rabbit model, small LDL was taken up into the aorta wall 50% faster in lesions and 90% faster in nonlesion areas compared with large LDL ($P < 0.01$) [43]. It was reported that a 5% smaller LDL diameter resulted in a 50% faster LDL uptake into the vessel wall. Second, thromboxane synthesis appears to be greater in LDL pattern B patients [44]. Third, sialic acid content is decreased and proteoglycan binding is greater in LDL pattern B compared with pattern A patients [45]. Fourth, small LDL size appears to be related to endothelial dysfunction [46•]. Fifth, vitamin E levels are reduced and oxidative susceptibility is increased in LDL pattern B patients. Sixth, enhanced postprandial lipemia has been linked to CHD risk, and LDL pattern B patients have greater postprandial lipemia compared with LDL pattern A patients [47•].

The first epidemiologic studies that investigated LDL subclasses and CHD had a cross-sectional design, but the findings in them were consistent with the more recent prospective trials. To date, 33 cross-sectional epidemiologic, 18 prospective epidemiologic [3,6–9,25–28,48–54,55••], and 8 clinical intervention trials [3,6,7,9,48,50,51,53] have examined the relationship of LDL particle size and CHD risk. Of the 33 cross-sectional studies reviewed, 25 (76%) demonstrated a significant univariate relationship between small-sized LDL particles and CHD [42••]. Of the 20 cross-sectional studies that utilized multivariate analysis of the relationship of small LDL size and CHD, 12 trials (60%) showed that the relationship with LDL size was not independent of TGs and/or HDL-C levels. Similarly, 16 of 18 (88.9%) prospective epidemiologic trials reported a significant univariate association of LDL size or density with CHD risk, although only 4 (22.2%) of these trials found this risk to be independent of other lipid risk factors (Table 1) [42••]. However, LDL size is seldom a significant and independent predictor of CHD risk after multivariate adjustment for confounding variables, in particular plasma TG levels and HDL-C concentrations. Therefore, it may be that the increased risk associated with smaller LDL size in univariate analyses is a consequence of the broader pathophysiology of which small, dense LDL is a part, rather than a reflection, of an isolated intrinsic increased atherogenic potential. This issue is analogous to the relationship of fasting TGs to CHD risk [56]. It remains unclear which specific characteristic or combination of characteristics of small, dense LDL particles is the most useful representative of vascular disease risk [57•]. The vast majority (but not all) shows a significant univariate association of small, dense LDL with increased CHD risk.

This issue is further complicated by the fact that at the same level of LDL-C, higher-risk LDL pattern B individuals have significantly more LDL particles than those with LDL pattern A. The number of LDL particles in plasma is potentially important, because the arterial walls are exposed to these particles, and an increased number might increase atherogenicity independent of particle size [58]. Is the higher risk of pattern B individuals attributable to the fact that they have more LDL particles in total, or does the smaller size contribute independently to CHD risk? Higher LDL particle concentrations seem to be important in determining CHD risk, and some studies have assessed whether the quantity rather than the size of small, dense LDL is more strongly associated with CHD risk [3,35,54,59•]. In these studies, the number of total and smaller LDL particles was a significant and independent predictor of CHD risk after multivariate adjustment for lipid variables [3,54,59•]. A 13-year follow-up of the Quebec Cardiovascular Study [60••] has confirmed that LDL-C of less than 255 Å has a strong and independent association with CHD in men that is particularly powerful over the first 7 years of follow-up. Williams et al. [61] found that the smallest LDL subclass, LDL-IVb, is the single best lipoprotein predictor of increased CHD progression in men, which is an unexpected result given that LDL-IVb represents only a minor fraction of total LDL in the 4-year Stanford Coronary Risk Intervention Project [61]. However, the Stanford observation supports the concept that small LDL is a particularly strong contributor to CHD risk.

LDL-Num and Cardiovascular Risk

LDL heterogeneity is also apparent in the variability of the number of LDL particles among individuals with the same LDL-C measurement. Due to the presence of one apoB-100 molecule per LDL and IDL particle, and because approximately 95% of apoB is bound to LDL particles in the normal physiologic state, total apoB is historically used to determine the number of LDL or atherogenic particles. ApoB-48 is derived from the intestines and primarily bound to TG-rich lipoproteins, such as found in the chylomicron and remnant lipoprotein. Standard laboratory determination of whole plasma apoB does not distinguish between apoB-48 and apoB-100. Nevertheless, whole plasma apoB is a powerful predictor of CHD risk [62].

Table 1. Prospective studies documenting the prediction of CHD risk by LDL size and/or particle number

Study / year	Population	CVD event	Method	LDL	Univariate analysis	Multivariate analysis
Watts et al. [8] / 1993	With hypercholesterolemia	CHD	GGE	LDL 3	Yes	Yes
Stampfer et al. [28] / 1996	Healthy physicians	CHD	GGE	LDL size	Yes	No
Gardner et al. [25] / 1996	Healthy people	CHD	GGE	LDL size	Yes	Yes
Miller et al. [6] / 1996	With CHD	Angiographic MLD	GGE	LDL size	Yes	No
Mack et al. [7] / 1996	With CHD and hypercholesterolemia	Angiographic MLD	ANUC	LDL size	Yes	No
Lamarche et al. [31] / 1997	Healthy men	CHD	GGE	LDL size	Yes	Yes
Ruotolo et al. [48] / 1998	Young survivors of MI	Atherosclerosis progression	GGE	LDL size	Yes	No
Mykkänen et al. [49] / 1999	Healthy elderly	CHD	GGE	LDL size, apoB	No	No
Zambon et al. [9] / 1999	Patients from FATS trial	CHD progression	GGE	LDL size	Yes	Yes
Austin et al. [41] / 2000	Older Japanese-American men	CHD	GGE	LDL size	Yes	No
Campos et al. [50] / 2001	MI survivors	Recurrent coronary events	GGE	LDL size	No	No
St-Pierre et al. [27] / 2001	Healthy men	CHD	NMR	LDL size	Yes	–
Vakkilainen et al. [51] / 2002	Diabetic patients with CHD	Atherosclerosis progression	GGE	LDL size, apoB	Yes	–
Rosenson et al. [3] / 2002	Healthy people	Angiographic MLD	NMR	LDL size, LDL-Num	Yes	Yes
Blake et al. [26] / 2002	Healthy women	CHD	NMR	LDL size, LDL-Num	Yes	No
Kuller et al. [54] / 2002	CHD patients vs healthy people	CHD	NMR	LDL size, LDL-Num	Yes	No
Wallenfeldt et al. [52] / 2004	Middle-aged men	Change in carotid IMT	GGE	LDL size	Yes	–
van Tits et al. [53] / 2004	With familial hypercholesterolemia	Atherosclerosis progression	GGE	LDL size	Yes	–
Otvos et al. [59•] / 2006	Healthy men	Nonfatal MI/CHD/death	NMR	LDL size, LDL-Num	Yes	–
El Harchaoui et al. [55••] / 2007	Healthy people	CHD	NMR	LDL size, LDL-Num	Yes	No

ANUC—analytic ultracentrifugation; apoB–apoprotein B; CHD—coronary heart disease; CVD—cardiovascular disease; FATS—Familial Atherosclerosis Treatment Study; GGE—gradient gel electrophoresis; IMT—intima-media thickness; LDL—low-density lipoprotein; LDL-Num—LDL particle number; MI—myocardial infarction; MLD—minimal lumen diameter; NMR—nuclear magnetic resonance.

A substantial body of evidence strongly suggests apoB should replace LDL-C as the primary measure of atherogenic lipoproteins [63]. ApoB has been identified as primarily two apoproteins that are immunologically distinct. The methodology is now standardized and a national apoprotein standardization program exists [64]. In the setting of normolipemia, plasma apoB values are consistently lower than the LDL-C value. However, the condition described as hyperapobetalipoproteinemia is characterized by apoB values higher than predicted based on the LDL-C value [65].

Because an increased number of LDL particles cosegregates with other CHD risk factors, multivariate analyses are required to establish whether LDL-Num is a statisti-

cally significant, independent predictor of clinical events. Rader et al. [66] and Sniderman et al. [35] reviewed 32 trials that studied the relationship between plasma apoB concentrations and CHD risk, but the data did not consistently support a stronger association between CHD risk and apoB (atherogenic particle number) than between CHD and other lipid parameters in this type of analysis.

In the Framingham Offspring Study, a "disconnect" between LDL-C and LDL-Num was noted among patients with elevated TG levels or low HDL-C levels, as would be expected in patients with the small LDL trait who would be concentrated in populations with either elevated fasting TGs or low HDL cholesterol. In those with HDL-C less than 50 mg/dL, LDL particle concentration was considerably higher than suggested by the LDL-C level because these patients had excess numbers of small LDL particles [29,67]. These data indicate that patients with type 2 diabetes mellitus and LDL-C levels less than 100 mg/dL are extremely heterogeneous with regard to LDL-Num and, by inference, LDL-based cardiovascular risk estimates. In the Framingham Heart Study [68•], increase in LDL-Num, especially small LDL, paralleled an increase in metabolic syndrome components in both men and women. The increase in small LDL particles was especially associated with increased TGs and decreased HDL-C, but was not reflected by changes in the concentration of LDL-C. Although increased small LDL-Num, as a single measure, is highly predictive of metabolic syndrome, a higher small LDL-Num was not associated with an increased CVD event rate in people with metabolic syndrome in this Framingham analysis [68•].

Results from four outcome studies, Cardiovascular Health Study [54], Women's Health Study [26], Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) [59•], and Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial [3], provide persuasive evidence that LDL-Num is a stronger predictor of incident CHD events or disease progression than LDL-C [26,59•]. In all of these studies, LDL-Num was independent of the standard lipid variables. LDL particle size was also a significant predictor in univariate analyses in three large studies: the Quebec Cardiovascular Study, the Harvard Physicians Health Study, and the Stanford Five City Project [25,28,31].

LDL Particle Size and Number Correlate with Change in Cardiovascular Risk

Studies have investigated whether therapeutic modification of LDL particle size and number reduces cardiovascular disease as defined by arteriographic change as the outcome variable. Without treatment, arteriographic coronary artery disease progression in the controls is significantly greater in patients with a predominance of small, dense LDL [3,6,7], and arteriographic benefit is concentrated in patients with a predominance of small, dense LDL who receive treatment that improves the LDL subclass distribution. These studies included the Stanford Coronary Risk Intervention Project (SCRIP) [6], the Familial Atherosclerosis Treatment Study (FATS) [9], the St. Thomas' Atherosclerosis Regression Study (STARS) [8], and the PLAC-I trial [3]. In all these studies, therapeutic modulation of LDL size was significantly associated with reduced CHD risk on univariate analysis. Under multivariate analysis with adjustments for confounding factors, changes in LDL size by drug therapy were the best correlates of changes in coronary stenosis in FATS [9]. In STARS, the smallest LDL fraction was the plasma lipoprotein subfraction, with the single most powerful effect on coronary artery disease regression in middle-aged men with hypercholesterolemia [8]. The SCRIP study reported that despite almost identical LDL-C reduction in patients with predominantly dense (pattern B) or buoyant (pattern A) LDL particles, there was no significant arteriographic change difference between treatment and control pattern A patients, whereas a significant reduction in the rate of arteriographic progression was seen in the treatment versus control dense LDL (pattern B) patients [6]. In PLAC-I, using a logistic regression model that adjusted for lipid levels and other confounding factors, elevated levels of small LDL were associated with a ninefold increased risk of coronary artery disease progression, but only in the placebo group [3]. In addition, in this study, elevated LDL-Num was a predictor of coronary artery disease progression after adjustment for race, sex, age, treatment group, baseline lumen diameter, and plasma lipids [3]. Thus, LDL pattern B CHD patients progress at a faster rate compared with LDL pattern A CHD patients, but with appropriate treatment the LDL pattern B patients have greater arteriographic benefit compared with LDL pattern A patients. This body of knowledge reflects the importance of lipoprotein subclasses in the atherogenic process that was first raised by Gofman and colleagues more than 50 years ago [10].

Conclusions

Because the cholesterol content per LDL particle exhibits large interindividual variation due to differences in particle size as well as relative content of cholesterol ester and TGs in the particle core, the information provided by LDL-C and LDL-Num is not equivalent [67]. Each measure provides information on atherogenic potential that is useful for diagnostic and therapeutic purposes. Measurements of LDL-Num and LDL size have the potential to improve coronary disease risk assessment as well as decisions about LDL treatment intensity, as they account for aspects of lipoprotein atherogenicity that are incompletely reflected by values of LDL-C. This knowledge impacts CHD risk prediction, clinical outcomes, and appropriate therapy selection for individual patients [17,69,70].

Disclosures

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The statistically significant benefit seen in LDL-C studies may not be clinically relevant, and these studies ignore other lipoprotein disorders contributing to CHD risk.

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