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CASE REPORT

Moving beyond LDL-C: incorporating lipoprotein particle numbers and geometric parameters to improve clinical outcomes

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Thomas Dayspring[1]
Tara Dall[2]
Majed Abuhajir[3]

[1]North Jersey Institute of Menopausal Lipidology, Wayne, NJ, USA; [2]Advanced Lipidology, Delafield, WI, USA; [3]Clinical Trials, Columbia-St Mary's Cancer Center, Milwaukee, WI, USA

Abstract: Lipoproteins are complex protein-enwrapped particles which traffic hydrophobic lipids and other molecules between tissues in plasma. Under a variety of pathological states, specific lipoproteins trafficking sterols, phospholipids, and fatty acids enter arterial walls enhancing a maladaptive inflammatory response resulting in atherogenesis. Several lipoprotein particle geometric parameters are now readily available from the laboratory. Such measurements beyond standard lipid concentrations can be used to better understand both the link between atherogenesis and the trafficking patterns of lipoproteins. Often, the various laboratory indices, especially standard particle lipid concentrations versus lipoprotein particle parameters, seem to conflict or exhibit discordance and thus confuse the patient and the provider. By using readily available (but often misunderstood) particle geometric parameters from two patients, we have attempted to illustrate that by properly utilizing the newer assays, very discordant standard lipid concentrations and lipoprotein laboratory parameters can be present in two specific patients and demonstrate how the newer parameters can aid the clinicians in performing better risk assessment and treatment decisions.

Keywords: lipoproteins, HDL-cholesterol, LDL-cholesterol, LDL particle number, HDL particle number, LDL composition, LDL size

Geometry is the mathematical science concerned with questions of size, shape, and relative position of objects and with properties of volume and space. Measurements of lengths, areas, and volumes have significant applicability when assessing the variable characteristics of discoid and spherical lipoprotein particles which traffic hydrophobic lipids through miles of vessels in the human body. Geometric characteristics and the content of lipoprotein cores have variable relationships to atherosclerotic cardiovascular disease (CVD) and risks.

Atherosclerosis is simply an accumulation of sterols in arterial wall macrophages, and the sterol depositors are specific, hereafter termed atherogenic lipoproteins. Traditional lab assays either calculate or directly measure particle core lipid concentrations (the amount of cholesterol or triglycerides [TG] within all or specific species of the lipoproteins that exist in a given volume of plasma usually reported in mg/dL or mmol/L) and then often incorporate those concentrations into ratios or other calculations. See Table 1 for definitions of standard lipid measurements and ratios which clinicians use to perform risk assessment and as goals of therapy.

A recent study of 136,905 patients hospitalized for coronary artery disease revealed almost half had an at goal low-density lipoprotein cholesterol (LDL-C) <100 mg/dL and 17.6% <70 mg/dL.[1] It is imperative that clinicians become familiar with now readily

Correspondence: Thomas Dayspring
North Jersey Institute of Menopausal Lipidology, 516 Hamburg Turnpike, Wayne, NJ 07470, USA
Tel +1 973 790 8604
Fax +1 973 790 1488
Email tdayspring@aol.com

Table 1 Standard lipid measurements or calculations

Measurement/ calculation	Description
TC	Cholesterol within all lipoproteins per deciliter (dL)
VLDL-C	Cholesterol within VLDLs/dL (calculated as TG/5) Indicative of remnants
IDL-C	Cholesterol within IDLs/dL. Not normally reported, but rather incorporated into LDL-C calculations
LDL-C calculated	Cholesterol within IDLs and LDLs and Lp(a)s/dL LDL-C = TC minus [HDL-C + VLDL-C] where VLDL-C = TG/5
LDL-C measured	Cholesterol within LDLs/dL
HDL-C	Cholesterol within all of the HDLs per dL
TG	TG within all lipoproteins/dL
Non-HDL-C	Cholesterol not in HDL particles/dL. Calculated as TC minus HDL-C. Non-HDL-C =VLDL-C + IDL-C + LDL-C + Lp(a)-C. Indicative of potentially atherogenic cholesterol
TC/HDL-C ratio	Often used as a risk factor or surrogate of apoB/apoA-I ratio
TG/HDL-C ratio	Used to estimate LDL particle size with a level >3.8 indicative of an 80% chance of small LDL particles

Abbreviations: apoA-I, apolipoprotein A-I; apoB, apolipoprotein B; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; LDL-P, LDL particle concentration; HDL, high-density lipoprotein; HDL-C, HDL cholesterol; HDL-P, HDL particle concentration; IDL, intermediate-density lipoprotein; IDL-C, IDL cholesterol; TC, total cholesterol; TG, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol.

available laboratory geometric lipoprotein parameters that can provide better information in both obvious and subtle ways on sterol (cholesterol and noncholesterol) trafficking and atherogenesis that can improve risk assessment and serve as more definitive goals of therapy. For over a decade now, providers also have had the ability to measure lipoprotein size in nanometers (nm) or angstroms (Å) and assign patients to large or small LDL phenotypes or patterns (A and B, respectively). One can also use diameter to calculate particle volumes and particle core cholesterol molecule concentration. Major position[2] and consensus statements[3,4] as well as evidence-based reviews[5] have emerged recommending methods available to measure particle concentrations (how many lipoproteins exist per unit of plasma volume) such as certain structural apolipoproteins, specifically apolipoprotein B (apoB) or apolipoprotein A-I (apoA-I) measurements, nuclear (proton) magnetic resonance (NMR) spectroscopy[6] or other, newer (and far less adjudicated) tests such as particle ultracentrifugation with staining or ion mobility transfer (see Table 2).

As useful as the standard lipid profile has been, it has shortcomings that prevent clinicians from doing an optimal job with assessing baseline or on-treatment (residual) atherosclerosis risk, especially in patients with cardiometabolic risk (insulin resistance).[7–9] Geometric analysis of lipoprotein parameters, especially LDL (Figure 1), provides many insights related to baseline and residual risk, not all

Table 2 Standard lipoprotein measurements

Measurement	Description
ApoB measurement	A measure of all of the apoB-containing lipoproteins in mg/dL
LDL-P	Number of LDL particles per liter (nmol/L)
ApoA-I	An estimate of HDL particle concentration (mg/dL)
Total HDL-P	All of the HDLs in µmol per liter of plasma except prebeta species
LDL size	Peak particle diameter of LDLs in nm
LDL phenotype or pattern	Large (A) or small (B)

Abbreviations: apoA-I, apolipoprotein A-I; apoB, apolipoprotein B; LDL, low-density lipoprotein; LDL-P, LDL particle concentration; HDL, high-density lipoprotein; HDL-P, HDL particle concentration.

of which are readily recognizable by examining measured and/or calculated lipid concentrations found in the standard lipid panel.

Multiple trials, including the Apolipoprotein-related Mortality Risk (AMORIS),[10] Women's Health Study (WHS),[11] Women's Health Initiative (WHI),[12] Framingham Offspring Study (FOS),[13] Multiethnic Study of Atherosclerosis (MESA),[14] European Prospective Investigation Into Cancer and Nutrition – Norfolk Study (EPIC-Norfolk),[15] INTERHEART,[16] Cardiovascular Risk in Young Finns Study,[17] Air Force/Texas Coronary Atherosclerosis Prevention Trial (AFCAPs-TexCAPS),[18] and others[19–22] have demonstrated that cardiovascular (CV) events are more related to atherogenic lipoprotein concentration as measured by apoB particle number or LDL particle number (LDL-P) than to cholesterol concentration estimates or assays of the content of various lipoprotein subfractions such as LDL-C, non-high density lipoprotein (HDL) cholesterol (non-HDL-C),[13]

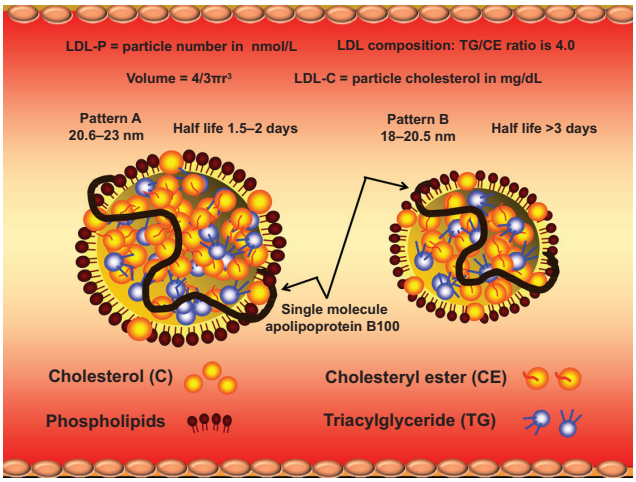

Figure 1 Low-density lipoprotein (LDL) geometric parameters: LDLs consists of a core of cholesteryl ester (CE), triglycerides (TG) surrounded by a phospholipid, free cholesterol surface enwrapped by a single molecule of apolipoprotein B100.

or the total cholesterol (TC)/HDL-C ratio.[23] What drives the apoB-containing lipoproteins into the arterial wall is particle number (apoB), not particle size or particle lipid content.[24] In April of 2008, the American Diabetes Association (ADA) and the American College of Cardiology (ACC) issued a consensus statement advocating that in patients with cardiometabolic risk in high or very-high risk categories, measured apoB assays or perhaps LDL-P using NMR be considered to better ascertain risk and serve as a goal of therapy in patients on drug therapy. The paper discussed the weakness of LDL-C in such patients and encouraged calculation of non-HDL-C with a reminder that although non-HDL-C correlates with apoB better than does LDL-C, correlation can also be moderately discordant in upwards of 30% of individual patients.[3] Because of its 2–3-day half-life, compared with the much shorter half-life of very-low-density lipoproteins (VLDLs) and intermediate-density lipoproteins (IDLs), LDL particles are the most prevalent apoB-containing lipoproteins present in plasma.[25] One way to evaluate, analyze, and compare lipid and lipoprotein concentrations is to relate them as a percentile level or cutpoint from a distribution analysis of reference populations like FOS or MESA, where the assumption is atherogenic lipid/lipoprotein concentrations in the lower percentile cutpoints are healthier than those in higher cutpoints. In FOS, the 20th percentile cutpoint of LDL-C is 100 mg/dL and LDL-P is approximately 1100 nmol/L of plasma.[26] See Table 3. An interesting and insightful, and to many an astonishing, exercise (Table 4) is to estimate how many LDL particles circulate in the entire plasma of a typical person. A male of normal weight and hematocrit with an LDL-P of 1100 (20th percentile cutpoint) would have ~1.782×10^{18} (quintillion) circulating LDL particles. Imagine a high-risk person in or above the 80th percentile cutpoint – there would be a formidable therapeutic task in normalizing the numbers. The clinical challenge is to understand that in many patients there may be little correlation (much discordance) between LDL-C and LDL-P values, and risk always follows particle concentrations (apoB or LDL-P).[2,13,27]

To elucidate some of the geometric concepts affecting lipid and lipoprotein concentrations and their use by clinical lipidologists, we will discuss two male patients, hereafter referred to as the Professor and the Provider. The former is a 77-year-old male with a past history of a myocardial infarction (MI) and hypercholesterolemia treated with a statin for many years. His current regimen is rosuvastatin 20 mg and ezetimibe 10 mg daily. The Provider is a 50-year-old overweight male, with a pretreatment history of the metabolic syndrome, taking rosuvastatin 20 mg, ezetimibe 10 mg, and fenofibrate 145 mg daily. Both have normal high-sensitivity C-reactive protein levels. Many might expect that these patients who are using such powerful combination treatment regimens would be at their lipid/lipoprotein goals. Applying the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP-III) recommendations, the Professor is an MI survivor (secondary prevention) who does not meet all of the criteria for a very high-risk patient but because of the MI must be considered high risk.[28,29] Using Framingham Risk Scoring, the Provider would be considered low risk, but because of his history of the metabolic syndrome many would elevate him to a moderate risk category.[8,24,30] Both patients, on-treatment, standard lipid concentrations, and NCEP ATP-III goals of therapy are shown in Table 5.

Table 3 Population comparisons of lipid and lipoprotein particle concentrations

	Framingham Offspring[a] n = 3367 (1367 men; 1732 women)			
Percentile	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	LDL-P (nmol/L)	ApoB (mg/dL)
2	70	83	720	54
5	78	94	850	62
10	88	104	940	69
20	100	119	1100	78
30	111	132	1220	85
40	120	143	1330	91
50	130	153	1440	97
60	139	163	1540	103
70	149	175	1670	110
80	160	187	1820	118
90	176	205	2020	130
95	191	224	2210	140

Note: [a]Specimens collected in 1988–1991 (exam cycle 4). Analysis restricted to subjects with triglycerides <400 mg/dL. Ethnic makeup 99% Caucasian.[20,42]
Abbreviations: apoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particle concentration.

Table 4 Human plasma LDL particle concentrations (male)

Blood volume (BV) = Plasma volume (PV)/1 – hematocrit (Hct)
In a male with 5 L[a] of BV and a Hct of 46%[a], PV = 2.7 L
1 nmol/L of LDL-P contains 6×10^{14} particles (six hundred trillion)
1000 nmol/L of LDL-P contains 6×10^{17} particles (six hundred quadrillion)
Framingham Offspring Study: the 20th percentile population cutpoint of LDL-P is ~1100 nmol/L (low risk) and the 80th percentile cutpoint is ~1810 nmol/L (high risk)
A male with and LDL-P of ~1100 nmol/L and 2.7 L of plasma has $6 \times 10^{14}(1100)(2.7)$ or 1782×10^{15} (quadrillion) or 1.782×10^{18} (quintillion) circulating LDLs
A male with an LDL-P of ~1820 nmol/L and 2.7 L of plasma has $6 \times 10^{14}(1820)(2.7)$ or 2948×10^{15} (quadrillion) or 2.984×10^{18} (quintillion) circulating LDL particles

Note: [a]Assumed for purposes of illustration only.
Abbreviations: LDL, low-density lipoprotein; LDL-P, LDL particle concentration.

Table 5 Lipid concentrations and ratios and goals of therapy

The Professor	NCEP ATP-III goals (high risk)	The Provider	NCEP ATP-III goals (moderate risk)
TC = 171[a]		TC = 125[a]	
HDL-C = 56[a]	No specific goal**	HDL-C = 48[a]	No specific goal[b]
LDL-C = 101[a]	<100 mg/dL (option for 70)	LDL-C = 65[a]	<130 mg/dL (option for 100)
TG = 72[a]	No specific goal**	TG = 59[a]	No specific goal[b]
VLDL-C = 14[a]		VLDL-C = 12[a]	
Non-HDL-C = 115[a]	<130 mg/dL (option for 100)	Non-HDL-C = 77[a]	<160 mg/dL (option for 130)
TC/HDL-C = 3.05		TC/HDL-C = 2.6	
TG/HDL-C = 1.3		TG/HDL-C = 1.2	

Notes: [a]Measurement in mg/dL; [b]If TG > 200, non-HDL-C becomes a secondary goal of therapy.
Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NCEP ATP-III, National Cholesterol Education Program, Adult Treatment Panel III; TC, total cholesterol; TG, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol.

With respect to the ATP-III goals of therapy: for a high-risk patient like the Professor, the NCEP ATP-III LDL-C goal is <100 mg/dL. The NCEP 2004 addendum offered an optional LDL-C goal of 70 mg/dL in high-risk patients.[28] Non-HDL-C would not be a factor because the on-treatment TGs are <200 mg/dL; however, newer data from Framingham have shown that non-HDL-C is always as good or out predicts LDL-C as a CVD risk factor whether TG are elevated or not.[31] The American Heart Association (AHA) secondary prevention guidelines advocate an LDL-C < 70 mg/dL in high-risk patients.[32] The Professor is not at the ATP-III optional goal or the AHA LDL-C goal of <70 mg/dL. The Provider is significantly below all of the guideline lipid goals for a moderate risk patient. Using the lipid concentrations, the case could be made for more aggressive treatment for the Professor and perhaps a reduction in the pharmacological therapy for the Provider.

As discussed in an international position paper,[2] the ADA/ACC consensus statement,[3] and a more recent statement from the American Association of Clinical Chemistry (AACC),[4] quantifying atherogenic lipoproteins is the best way to assess and treat CVD risk. There is one apoB molecule on each chylomicron, VLDL, IDL, and LDL particle. Because of the significantly longer LDL half-life compared with the other apoB particles, the vast majority (over 90%) of the apoB measurement represents LDL-P.[13,25] In the apoB protein immunoassay,[33] an antibody attaches to certain specific areas of the apoB molecule called epitopes, which are the three-dimensional areas on the surface of the apoB molecule. Using lipoprotein population cutpoints data from a reference population such as the FOS (Table 1), lower CV risk may be associated with concentrations that are in the bottom 20th percentile of the population and higher risk with those above the 80th percentile (top 20th percentile).[20,34]

The Professor's LDL-C of 101 mg/dL and his non-HDL-C of 115 mg/dL are at the 20th percentile FOS cutpoint. The Provider's LDL-C of 65 mg/dL, and his non-HDL-C of 77 mg/dL are below the second percentile (a cutpoint likely associated with little CV risk; an LDL-C of <70 mg/dL is the second percentile cutpoint in FOS). Although, in general, non-HDL-C correlates well with apoB and LDL-P levels, that correlation can be moderately discordant in individual patients.[3,4,35] It would be reasonable to surmise that since the therapies have achieved NCEP ATP-III goals, the treatment should prove successful and have little residual risk. One might want to get more aggressive in the high-risk Professor to strive for the optional LDL-C goal of <70 mg/dL, and one might consider reducing the lipid-modulating therapies used by the Provider. Yet, both the ADA/ACC and AACC statements warn us that if lipoprotein particle concentrations are elevated and not concordant with the lipid values, residual risk may yet be present.

NMR spectroscopy provides a different way to both quantify and examine other specific geometric particle parameters such as particle size, volume, and cholesterol composition. The NMR technology both sizes and quantifies lipoprotein particles by analyzing spectral signals produced by the terminal methyl groups on the lipid molecules within the particles; the number of methyl groups on TG, cholesterol, and phospholipid molecules are constant within a particle of a given size.[6] Both patient's NMR lipoprotein parameters are displayed in Table 6.

A convenient way of stratifying patients lipoprotein particle concentration is according to their percentile distribution cutpoint in a known population such as FOS or MESA. The LDL-P values of both patients are above the 20th percentile of FOS population cutpoints and suggest residual risk may yet be present despite the at-goal lipid concentrations. One might believe the NMR data is in error or perhaps not meaningful and simply dismiss the findings. However, in several studies including the WHS,[11] the WHI,[12] Veterans

Table 6 NMR lipoprotein patient parameters and population cutpoints

	Professor	Provider	Interpretation
LDL-P	1428 nmol/L	1647 nmol/L	~1100 nmol/L[a]
Small LDL-P	1191 nmol/L	1628 nmol/L	
LDL size	20.3 nm	19.1 nm	Large > 20 .5 nm, small ≤ 20.5 nm
Large VLDL-P	0.5 nmol/L	0.6 nmol/L	<0.5 nmol/L[b]
Large HDL-P	8.6 μmol/L	2.4 μmol/L	>9.0 μmol/L[b]

Notes: [a]FOS 20th percentile cutpoint value; [b]MESA 20th percentile cutpoint value.
Abbreviations: FOS, Framingham Offspring Study; LDL, low-density lipoprotein; LDL-P, LDL particle concentration; HDL-P, high-density lipoprotein particle concentration; MESA, Multiethnic Study of Atherosclerosis; NMR, nuclear magnetic resonance; VLDL-P, very-low-density lipoprotein particle concentration.

Affairs HDL Intervention Trial (VA-HIT),[36] as well as the Framingham Offspring study[13,37] and other trials,[38,39] LDL-P was more accurate than LDL-C in predicting CVD risk, and dismissal of the NMR parameters would be premature. Both of these patients also had Pattern B, LDL phenotype (small particles with a diameter ≤20.5 nm). Instead of being below the 20th percentile FOS cutpoint, the Professor's LDL-P of 1428 nmol/L is in the 45th percentile of the FOS population and the Provider's LDL-P of 1647 nmol/L is in the 65th percentile. The AACC statement[4] provides an on-treatment LDL-P goal of <1100 nmol/L for high-risk patients, as higher LDL-P concentrations are known to be predictive of CVD events regardless of LDL-C. Therefore, since the LDL-P levels are not optimal, and above the AACC goals, it is not unreasonable to assume that both patients still have residual risk despite the acceptable lipid concentrations. Indeed, such residual risk was evident in the LDL-P, LDL-C, and non-HDL-C analysis of the FOS.[13]

How could these patients have increased numbers of LDL particles despite having such at-goal cholesterol concentrations? LDL-C is simply the amount of cholesterol in milligrams that is transported within all of the LDL particles that exist in a deciliter of plasma. LDL-P is a measure of how many LDL particles are present in a liter of plasma, and as outlined, several studies have shown that not uncommonly there is discordance between LDL-C and LDL-P values. LDL particles are spherical: the geometric formula to calculate the volume of a sphere is 4/3(pi) radius cubed ($4/3\pi r^3$). Since volume is related to the third power of the radius, very small diameter (radius) changes can translate into significantly more or less ability to carry core cholesterol molecules. The phospholipid surface of a lipoprotein typically represents ~2 nm of the diameter, with the rest being determined by the particle core. It takes more cholesterol-depleted than cholesterol-rich LDLs to traffic a given mg/dL level of LDL-C (see Figure 1). Thus even if a radius of an LDL particle changes by a very tiny amount, say 0.5 nm, that subtle volume change significantly affects how many cholesterol molecules that LDL particle can traffic. Patients having LDLs that traffic more cholesterol molecules compared with those patients with LDLs trafficking less cholesterol molecules will have higher LDL particle counts (apoB) and thus higher CV risk. Many providers would not suspect that such a miniscule change in particle volume (radius) could have (translate into) such a profound effect on LDL-P (apoB).

It is relatively simple to calculate how many cholesterol molecules are in each LDL particle: simply divide LDL-C (in mol/L) by LDL-P (in mol/L).[13] We can calculate this rather easily if we convert their LDL-C value to a molar concentration and then simply divide it by the particle number (also in molar concentration). A mole of a substance contains 6×10^{23} molecules or atoms (Avogadro number). To convert units of mg/dL of cholesterol to millimoles per liter (mmol/L), multiply by 0.0259. A mole contains 10^3 mmol (a thousand millimoles), 10^6 μmol (a million micromoles), or 10^9 nmol (a billion nanomoles) (Figure 2).

Thus, patients with cholesterol-depleted LDL particles (usually small LDLs or TG-rich, cholesterol-poor LDLs of any size) often have elevated LDL-P or apoB. It must be recognized that it is not particle size but rather particle number that is the more important risk factor and that most patients with small or cholesterol-depleted LDLs will have an elevated apoB and LDL-P.[14,15,19] The volumes of the LDL particles in the cases under discussion are depicted in Table 7.

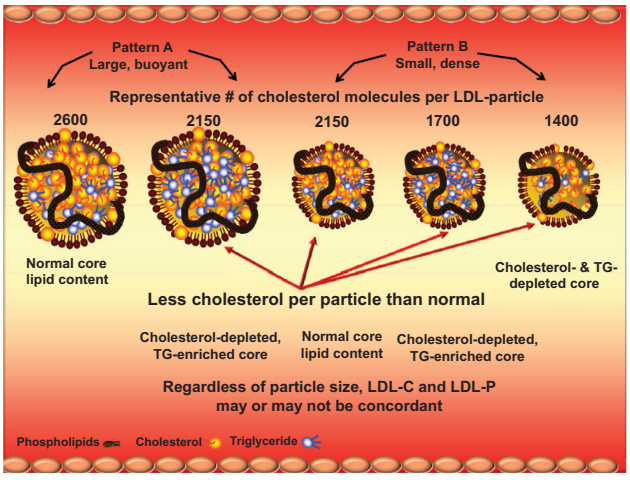

Figure 2 Low-density lipoprotein (LDL) composition: depending on LDL particle size and composition, LDL cholesterol and LDL particle number may or may not be concordant. Depending on the cholesterol/triglyceride (TG) composition, both large and/or small particles may be cholesterol depleted, which will therefore require more LDL particles to traffic a given amount of cholesterol.

Table 7 LDL particle volume calculation[a]

	Professor	Provider
LDL diameter (nm)	20.1	19.1
LDL radius (nm)	10.05	9.55
LDL volume calculations ($4/3\pi r^3$)	$4/3(3.14)(10.15)^3$	$4/3(3.14)(9.55)^3$
LDL volume cubic nm	4251	3648

Note: [a]Not adjusted for diameter of phospholipid coat.
Abbreviation: LDL, low-density lipoprotein.

Because of size differences, the Provider's LDL particles hold significantly less cholesterol molecules than the Professor's which have 17% more volume. This makes it easy to understand why patients with smaller, cholesterol-depleted LDLs need more particles to traffic a similar cholesterol load and why so many patients with LDL phenotype B (small size) have increased LDL-P.

Since the Professor's LDLs each traffic ~1800 molecules of cholesterol compared with the Provider's ~1100, each of the Provider's LDLs are significantly more cholesterol depleted (by 36%) than the Professor's (alternatively the Professor's LDLs are 57% more cholesterol rich) (see Table 8).

Paradoxically, despite having the lower LDL-C, the Provider requires significantly more LDL particles to traffic his LDL-C of 65 mg/dL than does the Professor with a much higher LDL-C of 101 mg/dL. Because of their 17% larger volume, the Professor's LDLs are capable of transporting significantly more (57%) cholesterol molecules per particle than are the Provider's. Particle diameters and lipid composition differences (TG/cholesterol ratio) are the major reasons explaining significant discordance between LDL-P (and apoB) and LDL-C (see Figures 1 and 2). A normal LDL particle has a core cholesteryl ester (CE) to TG ratio of 4:1. In a study of 100 healthy men and women, 21% had higher ratios, indicating that their LDLs were cholesterol-depleted, which demonstrates that even accurate LDL-C values will miss 20% of patients with elevated LDL-P.[40] Since the major determinant that drives the LDLs into the arterial wall is particle number (not particle size per se or particle cholesterol content),[2,24] it is easy to see how these two patients with good (Professor) and fabulous (Provider) LDL-C concentrations still can have residual risk associated with the still elevated LDL-P, but not identified by their LDL-C or even non-HDL-C levels. Metabolic syndrome, obesity, impaired fasting glucose, increased hepatic and endothelial lipase activity, increased CE transfer protein (CETP) activity are all associated with TG-rich lipoproteins and increased lipolysis of LDLs leading to both particle size reduction and core cholesterol depletion. One should keep in mind that if either of the patients under discussion had higher TG levels, more CETP-mediated TG entry into their LDLs would have further lowered their LDL particle cholesterol molecule concentration resulting in TG-rich, cholesterol-depleted LDLs (regardless of the LDL particle size). Such a scenario will also be associated with elevated apoB or LDL-P.[13,41–43] Indeed, the Ludwigshafen Risk and Cardiovascular Health Study showed that alterations of LDL metabolism characterized by high core LDL-TG were related to CAD, elevated high-sensitivity C-reactive protein, and vascular damage. High LDL-TGs were indicative of CE-depleted LDL, and elevated apoB, thus suggesting LDL-TG may better reflect the atherogenic potential of LDL than does LDL-C.[44] In the reality of the clinical world, one can only speculate as to the exact factors that might affect particle composition that are at play in a given patient. In a study looking at samples from 2355 type 2 diabetes mellitus patients with LDL-C $<$ 100 mg/dL, the data was extremely heterogeneous with regard to LDL-P and, by inference, LDL-based CV risk. Eighty-four percent of the patients with an LDL-C between 70 and 100 mg/dL (less than the MESA 20th percentile population cutpoint) had an LDL-P $>$1000 nmol/L (above the MESA 20th percentile population cutpoint). Astonishingly, 40.1% with an LDL-C $<$ 70 (well below any goal) mg/dL had an LDL-P $>$1000 nmol/L. Although there was more discordance in the high TG patients, even for patients with low TG distribution, there was considerable heterogeneity between LDL-C and LDL-P. One simply cannot use the "crutch" of hypertriglyceridemia to explain the discordance.[45]

Table 8 Cholesterol molecule per LDL particle calculation (estimates)

	Professor	Provider
LDL-C (mg/dL)	101	74
LDL-C (mmol/L) [(mg/dL 0.0259)]	2.61	1.91
LDL-C (mol/L)	2.61×10^{-3}	1.91×10^{-3}
LDL-P (nmol/L)	1428	1647
LDL-P (mol/L)	1428×10^{-9}	1647×10^{-9}
# cholesterol molecules per particle (LDL-C/LDL-P) each in mol/L	~1800	~1100

Abbreviations: LDL, low density lipoprotein; LDL-C, LDL cholesterol; LDL-P, LDL particle concentration.

There are many concept similarities between the LDL particle and HDL particle geometric principles and parameters in these patients. Looking simply at the HDL-C levels, the Professor has 12 mg/dL more of HDL-C than the Provider. Recent data has indicated that apoA-I, a surrogate of HDL particle number (HDL-P) might be a more important risk-related parameter than HDL-C.[46] One might assume that the patient

Table 9 HDL concentration parameters

	Professor	Provider
HDL (mg/dL)	56	48
Large HDL (μmol/L)	8.6	2.4
Medium HDL (μmol/L)	4.6	10.8
Small HDL (μmol/L)	25.1	27.9
Total HDL (μmol/L)	38.3	41.1

Abbreviations: HDL, high-density lipoprotein; HDL-C, HDL cholesterol; HDL-P, HDL particle concentration.

with the higher HDL-C has more HDL particles. Let's carefully examine HDL geometry in the two patients (Table 9).

Using the MESA population, HDL cutpoint data (personal correspondence with James Otvos of LipoScience); a total HDL-P of 38 μmol/L is in the 75th percentile cutpoint; that is, both patients have plenty of HDL particles. Note that since HDLs are measured in micromoles per liter (μmol/L) and apoB particles in nanomoles per liter nmol/L, humans have significantly more HDL particles than they do apoB particles (the difference between nanomoles and micromoles is a thousandfold [10^3]). Despite having the lower HDL-C and having a very low, large HDL-P value, the Provider has a higher total HDL-P than the Professor. The obvious difference is that the Provider has larger numbers of medium and small (delipidated) HDL particles. The likely explanation is that the Provider is taking a fibrate, a very effective drug at inducing hepatic production of apoA-I (a peroxisome proliferator-activated receptor-α-mediated process) and also inducing upregulation of hepatic scavenger receptors B1 (SR-B1), which bind to and delipidate larger, more mature HDLs causing them to shrink in size.[47] This phenomenon was seen in the Fenofibrate Intervention and Event Lowering in Diabetes study with fenofibrate[48] as well as in the VA-HIT trial using gemfibrozil. Robins proposed that the resultant delipidated smaller HDL species would have more capacity to further delipidate the arterial wall foam cells enhancing macrophage reverse cholesterol transport.[49] Therefore, because of fibrate-induced HDL delipidation, there will often be discordance between changes in HDL-C and HDL-P with the latter increasing more than the former. If the HDL particles are functional, it is conceivable that increased HDL-P or apoA-I may be a more important parameter to follow than is HDL-C.[46] Such a hypothesis would have to be tested in appropriate clinical trials. Since no such HDL functionality assay is available for routine clinical use, we are unable to evaluate the functionality of either patient's HDL particles.

Utilizing the concepts discussed in this paper, one should consider the very real world question: can the lipoprotein geometry be helpful in the clinic setting? Should clinicians tell these gentlemen that because their traditional lipid concentrations are at NCEP ATP-III goal, the residual risk (high LDL-P) potentially indentified by the NMR technique is not meaningful, or do we take note that when discordant, in many cited studies, LDL-P was a better predictor of CVD events, than were LDL-C and non-HDL-C and therefore advise both patients that further therapeutic endeavors may be needed? We believed it not unreasonable that the Professor should increase his dose of rosuvastatin to 40 mg and continue the ezetimibe and that the Provider should get more aggressive with therapeutic lifestyle changes (TLC) and/or perhaps add extended release niacin to his regimen. The niacin, through numerous mechanisms of action, when combined with a statin will further reduce apoB and TG-rich lipoproteins.[50] On follow-up, after receiving the 40 mg dose of rosuvastatin, the Professor's lipid profile was: TC = 121, HDL-C = 48, LDL-C = 68, and TG = 27 (all in mg/dL). The higher dose of rosuvastatin reduced both the LDL-C and the HDL-C (previously 56 mg/dL). That is not necessarily a concern as some therapies that dramatically lower total cholesterol (an apoB surrogate) can reduce HDL-C and apoA-I. This has been reported with both atorvastatin and rosuvastatin in high doses[51] and with the Ornish very low saturated fat diet (which is associated with angiographic benefit despite the dropping HDL-C in some patients).[52,53]

The Professor's lipoprotein concentrations on the higher dose (40 mg) of rosuvastatin are shown in Table 9. The dose increment by upregulating additional LDL receptors significantly improved total LDL-P to below the FOS 20th percentile cutpoint (Table 10).

The total HDL-P and the HDL-C dropped with the higher rosuvastatin dose. As noted above this has been seen in rosuvastatin clinical trials at 40 mg and with atorvastatin at the 80 mg dose.[54,55] Conceivably, the upregulated LDL receptors (as is seen with larger doses of statins), can endocytose additional apolipoprotein E-containing, HDL particles. Data from JUPITER (Justification for the Use of Statins in

Table 10 Professor's initial and follow-up lipoprotein parameters

	Initial	After rosuvastatin
Total LDL-P (nmol/L)	1428	983
Small LDL-P (nmol/L)	1191	971
LDL size (nm)	20.3	19.1
Large VLDL-P (nmol/L)	0.5	0
Large HDL-P (μmol/L)	8.6	8.6
Total HDL-P (μmol/L)	38.3	37

Abbreviations: HDL-P, high-density lipoprotein particle concentration; LDL, low-density lipoprotein; LDL-P, LDL particle concentration; VLDL-P, very-low-density lipoprotein particle concentration.

Prevention: an Intervention Trial Evaluating Rosuvastatin) patients using 20 mg of rosuvastatin showed no relationships between quartiles of HDL-C and baseline or on-treatment risk. ApoA-I was related to outcomes in the placebo group but not the rosuvastatin,[56] enforcing the NCEP ATP-III decision not to provide a specific HDL-C goal of therapy other than to normalize LDL parameters.[23]

With respect to the Provider, he increased TLC and lost 15 pounds and also started and then titrated extended-release niacin to a 2000 mg daily dose. Follow-up lab studies which are listed in Table 9 reveal there was a significant reduction in LDL-P (now 1182 nmol/L), additional reduction in LDL-C (54 mg/dL), a reduction in large and other VLDL-P species but also a reduction in HDL-C (from 48 to 40 mg/dL), with a slight increase in total HDL-P. Note that the LDL-P (now approaching the FOS 20th percentile cutpoint) and the LDL-C (below the second percentile FOS cutpoint) and are still widely discordant (Table 11).

These two cases represent a fascinating glimpse into the complex relationships between lipoprotein-associated lipid concentrations (standard lipid panel), lipoprotein particle concentrations, and geometric parameters of particle size, volume, molecular cholesterol content, as well as core TG-compositions. Particle geometry can offer insights to help explain the discordance between lipoprotein particle numbers versus standard particle lipid measurements or calculations and why lipid concentrations so often fail to identify baseline or residual risk. Such discordance can come into play in any individual patient (like the Professor) but are more common in insulin-resistant patients such as those with cardiometabolic risk (like the Provider). With rare exceptions (type III dyslipoproteinemia) when discordance is present, risk always follows particle concentrations.[13] The point of this manuscript is to inform readers that with respect to adjudicating CV risk or achieving a goal of therapy the ADA/ACC[3] and AACC[4] now recommend atherogenic particle counts (apoB or LDL-P) as providing more important information regarding baseline and residual CV risk than do standard lipid concentrations (LDL-C and non-HDL-C). It is unfortunate that the majority of providers are unaware of these new consensus statements. We are not proposing that clinicians should calculate all of the geometric parameters we discussed, but rather have an understanding of how the concepts of particle geometry explain the significant discordance between lipid concentrations (normal LDL-C and non-HDL-C) and atherogenic lipoprotein concentrations (high apoB and LDL-P). If these parameters did not influence LDL-P or apoB, they would be of little importance. We hope our article helps clinicians understand why so many patients have perfect LDL-C and non-HDL-C values but still have risk due to abnormal atherogenic particle concentrations.

Finally, the tests we used in the case discussion and that the ADA/ACC and AACC consensus statements recommend are apoB or LDL-P. Lipoprotein analysis by NMR spectroscopy is FDA approved (no longer considered experimental) and is now the most frequently ordered advanced lipoprotein test done in the United States. It is readily available in all 50 states and covered by Medicare and many other insurance companies. In addition to the standard lipid panel and LDL-P, all of the geometric parameters discussed in this paper are either reported (LDL particle size in nm) or can be easily calculated (particle volume, particle cholesterol molecule content) using simple formulas without any additional cost. ApoB is likewise universally available and costs no more than a lipid panel.

Table 11 Provider's initial and follow-up lipoprotein parameters

	Initial	After TLC and niacin
Total LDL-P (nmol/L)	1647	1182
Small LDL-P (nmol/L)	1628	1174
LDL size (nm)	19.1	18.8
Large VLDL-P (nmol/L)	0.6	0
Large HDL-P (μmol/L)	2.4	2.1
Total HDL-P (μmol/L)	41.1	42.9

Abbreviations: HDL-P, high-density lipoprotein particle concentration; LDL, low-density lipoprotein; LDL-P, LDL particle concentration; TLC, therapeutic lifestyle changes; VLDL-P, very-low-density lipoprotein particle concentration.

Disclosures

In the last 12 months, Thomas Dayspring has consulted for Abbott Labs, Genetech, Glaxo-Smith-Kline, Kowa, and Merck, and is on the advisory boards of Daiichi Sankyo, LipoScience, and Health Diagnostic Labs, and on the speakers bureau for Abbott, Merck, Glaxo-Smith-Kline, Kowa, Schering Plough, and Solvay. Tara Dall has consulted for Abbott, is on the speakers bureau for Abbott, AstraZeneca, Glaxo-Smith-Kline, LipoScience, Merck, Schering Plough, Solvay, and Takeda. Majed Abuhajir is on the speakers bureau of Celgene, Glaxo-Smith-Kline, and Novartis.

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