THOROUGHLY UNDERSTANDING THE LIPID PROFILE IN WOMEN:
**A Primer on Lipids, Lipoproteins and the Lipid Profile**

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Recognizing risk for and making the diagnosis of the many clinical expressions of atherosclerosis is no longer the sole responsibility of the internist or cardiologist. With the aging of the population, primary care providers, including gynecologists, must become fluent in the current understanding, diagnosis and initial therapies to combat atherosclerosis, the leading cause of morbidity and mortality in women. Several gynecologists have become diplomates of the American Board of Clinical Lipidology. The five major cardiovascular risk factors are age, hypertension, family history, cigarette smoking and lipid abnormalities. This paper will deal exclusively with the latter and attempt to help clinicians understand the meaning of each and every lipid concentration parameter reported within the standard lipid profile as well as the newer measures of lipoprotein quantification. There is only one absolute in atherosclerosis: sterols, predominantly cholesterol [Figure 1], must enter the artery wall and be oxidized and then internalized by macrophages, forming foam cells (the histological hallmark of atherosclerosis). Accumulation of foam cells results in fatty streaks and ultimately complex plaque. Lipids associated with cardiovascular disease (CVD) include cholesterol and noncholesterol sterols (e.g. sitosterol, campesterol, and others of mostly plant and shellfish origin), triacylglycerol or triglycerides (TG), and phospholipids.

Insert Figure 1

3-hydroxycholesterol
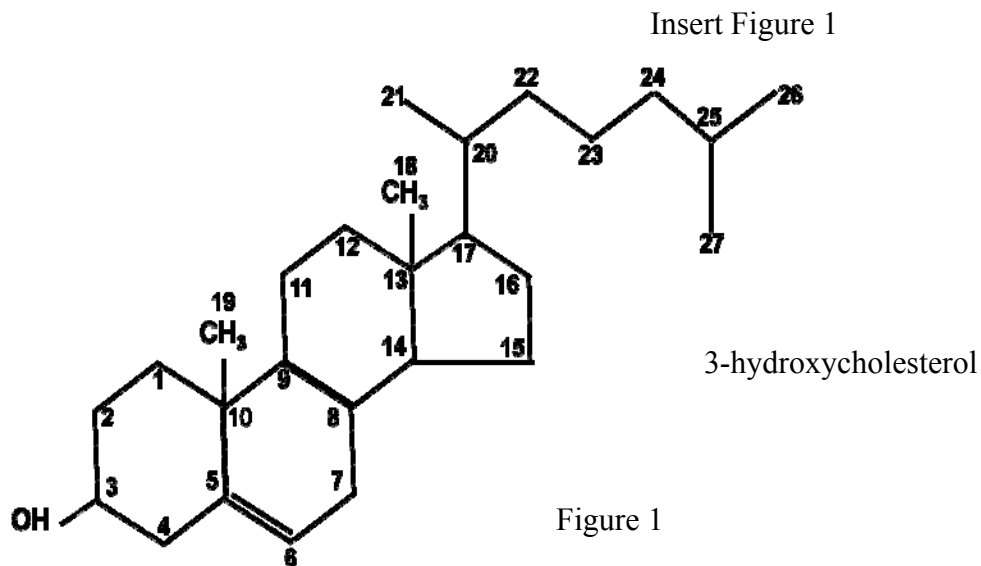
Figure 1

Since lipids are not very soluble in aqueous solutions like plasma they must be trafficked within protein enwrapped particles called lipoproteins which function as "lipid transportation vehicles" [Figure 2]. The surface proteins which provide structure and solubility to lipoproteins are called apolipoproteins. A key concept is that certain lipoproteins with their surface apolipoproteins and cholesterol core, are the agents of atherogenesis in that they transport the sterols into the arterial wall.[1] Diagnosing and treating CVD risk involves either quantitating atherogenic lipoproteins or estimating their presence by carefully analyzing all of the standard lipid concentrations and their various ratios. Successful prevention or treatment of

atherosclerosis then involves reducing the presence of atherogenic lipoproteins. Think of lipoproteins as variably sized "dump trucks": quantification refers to the number of dump trucks and lipids such as cholesterol concentrations refer to the amount of cholesterol collectively carried within the dump trucks in a deciliter of plasma. In a given patient's plasma, dump truck number required to traffic a given level of lipids would be related to their size and amount and types of lipids carried in each truck. Thus two women might have very different numbers of dump trucks even though they have the same amount cholesterol being transported. The dump truck analogy will be used throughout the paper and to simplify understanding the terms with lipoproteins and dump trucks being interchangeable terms. This analogy can also help clinicians explaining lipid complexities to laymen.

Lipoprotein measurement:

Lipoprotein particles have several defining characteristics, including lipid composition (TG vs. cholesterol content), size, as well as distinct surface apolipoproteins that are related to particle function and potential atherogenicity. Lipoproteins less than 70 nanometers (nm) in diameter, regardless of lipid composition are driven into the arterial intima primarily by concentration gradients.[2]
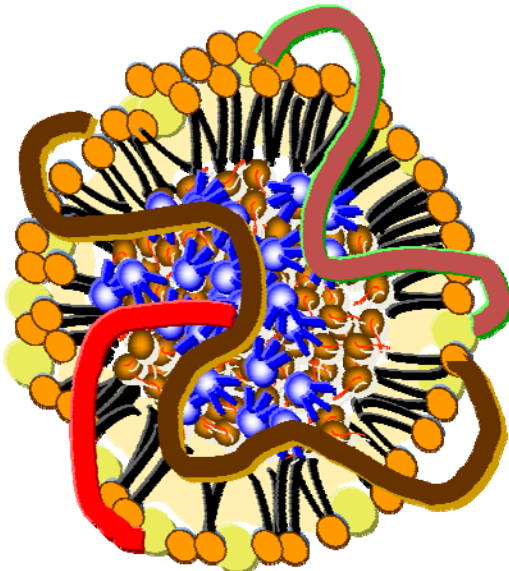

Figure 2

Typical lipoprotein with core of triglycerides (blue), sterols (gold), surface phospholipids, and snakelike apolipoproteins

Quantitating these potentially atherogenic lipoproteins, rather than assaying their lipid content, is now recognized to be the best lipid-related determinant of CVD risk and particle concentrations have emerged as not only superb predictors of risk, but also as desirable goals of therapy.[3,4,5,6,7] For a variety of logistical reasons including availability, cost, third party reimbursement and lack of interpretive knowledge, only a minority of clinicians routinely order lipoprotein quantification tests on their patients. Historically CVD risk and goals of therapy were based on lipid concentrations (the amount of lipids trafficked within lipoprotein cores). Guideline recommendations, including the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP-III) [6,8] and the American Heart Association CVD

Prevention in Women [9,10] use lipid concentrations like Total Cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C) and TG as estimates or surrogates of lipoprotein concentrations [Table I]. Think of LDL-C or HDL-C as the amount of cholesterol being trafficked by all of the LDL or HDL dump trucks in a deciliter of plasma. It has been assumed that if the lipid concentrations are in the desirable range, then atherogenic lipoproteins are unlikely to be present. However, the day has arrived when lipoprotein concentrations are replacing lipid concentrations in guidelines and clinical practice,[7] thus making it essential that clinicians develop solid understanding of lipoprotein physiology and pathology.[5,11] For those not using lipoprotein assays, it is crucial that one be as skilled as possible in accurately predicting the presence of atherogenic lipoproteins by using all of the lipid concentration parameters and ratios present in the lipid panel. The National Heart Lung and Blood Institute is over the next 18 months formulating new interpretive cardiovascular guidelines which will make the current ATP-III recommendations obsolete and at the present time providers would be more current following both the latest AHA Women's guidelines[10] and the new consensus statement from the American College of Cardiology and American Diabetes Association on lipoprotein management in patients with cardiometabolic risk.[7] [Table 4]

TABLE 1
AHA Women's Guideline Desirable Lipid Values

TC < 200 mg/dL
LDL-C < 100 mg/dL
HDL-C ≥ 50 mg/dL
TG < 150 mg/dL
Non-HDL-C < 130 mg/dL

For Very High Risk Patients
LDL-C < 70 mg/dL
Non-HDL-C < 100 mg/dL

Lipoproteins can be separated by several available methodologies including ultracentrifugation, electrophoresis, immunoassays of apolipoprotein content and nuclear magnetic resonance (NMR) spectroscopy. Of these techniques, only the latter two provide particle concentrations.[12,13] Using apolipoproteins, there are two major categories of particles: those historically termed alpha-lipoproteins or HDLs, which usually contain two to four molecules of apolipoprotein A-I (apoA-I) and the beta-lipoproteins, a collective group of chylomicrons, very-low density lipoproteins or VLDL, intermediate density lipoproteins or IDL, and LDL, each containing a single molecule of apolipoprotein B (apoB), [Figure 3].

Figure 3

Phospholipids ➷   Triglyceride 🜃   Cholesteryl ester 🜄
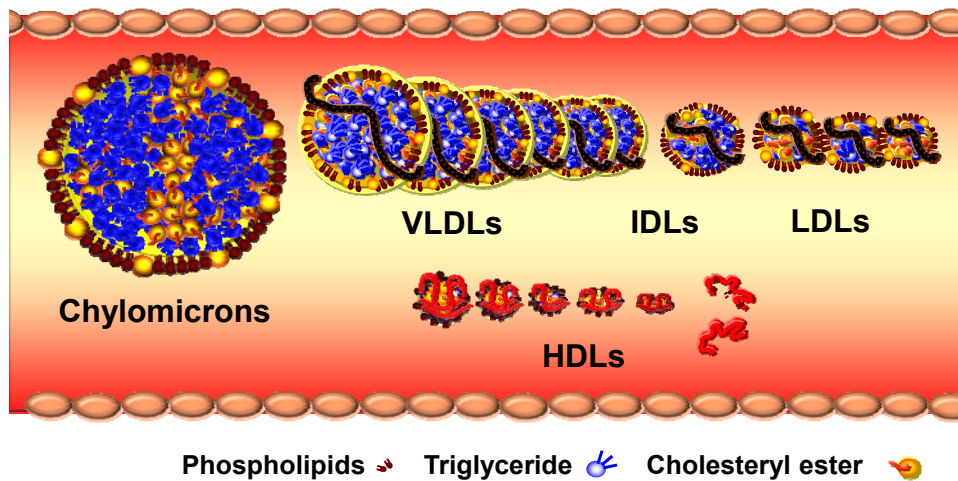
> Lipoproteins are a heterogeneous mixture of various sized particles with differing core lipid composition and concentrations. The apoB-containing lipoproteins are intestinally produced chylomicrons, and hepatic produced VLDLs and its catabolic products IDLs and LDLs and the apoA-I containing lipoproteins are the HDLs.

Because of very different half life's (VLDL: 2-6 hours, IDL: 1-2 hours, LDL: 2-3 days) the vast majority (> 90%) of apoB-containing particles are LDLs. Thus, although apoB measurement provides a collective quantification of all beta-lipoproteins it is primarily representative of LDL particle concentration (LDL-P). [14] Individual particle concentrations, determined by NMR spectroscopy are reported as VLDL-P, IDL-P, LDL-P and HDL-P.[13] [Table 2]

Several epidemiological studies enrolling both genders show that the best lipid-related predictors of risk in both men and women are elevated levels of apoB or LDL-P and reduced levels of apolipoprotein apoA-I or HDL-P or by combining both in the apoB/A-I ratio or LDL-P/HDL-P ratio.[4,12,13] Of importance is recent data from the Framingham Offspring Study where LDL-P was strongly associated with increased CVD risk in men and especially in women with LDL-P being twice as strongly related to CVD incidence. LDL-C was only modestly associated with CVD in women. Those within the lowest quartile LDL-P had significantly fewer events than those with equivalently low LDL-C or non-HDL-C.[14] Once one adjusts for lipoprotein concentration data (apoB or LDL-P), other lipoprotein characteristics such as particle size or lipid composition, for the most part, have no statistically significant relationship with CV risk. Thus small dump trucks are not more dangerous (atherogenic) than large ones, it simply takes more small than large trucks to traffic a given level of cholesterol. [8, 16,17]

TABLE 2 LIPID AND LIPOPROTEIN DEFINITIONS

TG is the triacylglycerol concentration within ALL of the TG-trafficking lipoproteins in 100 ml or
        a deciliter (dL) of plasma
TC is the cholesterol content within every lipoprotein in a deciliter of plasma
LDL-C is the cholesterol content within all the IDL and LDL particles in a dL of plasma
HDL-C is the cholesterol content within all of the HDL particles in a dL of plasma
VLDL-C is the cholesterol content within all of the VLDL particles in a dL of plasma
Remnant-C is the cholesterol content of all of the remnants in a dL of plasma
(Note NCEP recommends using VLDL-C as your surrogate of remnant-C)
Lp(a)-C is the cholesterol content of LDL particles that have apo(a) attached
Lp(a) concentration is the concentration of apo(a) in a dL of plasma
Non-HDL-C is the cholesterol within all of the apoB particles in a dL of plasma

LDL-P is the number of LDL particles in a liter of plasma (expressed in nmol/L): this represents all
        sized LDL particles: large or small
Small LDL-P is the number of small and intermediate LDL particles per liter of plasma (nmol/L)
HDL-P is the number of HDL particles in a liter of plasma (umol/L)
HDL-P is also reported as Large, Intermediate and Small HDL-P (umol/L)
VLDL-P is the number of VLDL particles in a liter of plasma (nmol/L)
IDL-P is the number of IDL particles in a liter of plasma (nmol/L)
LDL size is the diameter of the predominant LDL species
ApoA-I is the collective concentration of all of the apolipoprotein A-I containing lipoproteins
ApoB is the collective concentration of all of the apolipoprotein B containing lipoproteins
Pattern or phenotype A refers to predominantly larger, buoyant LDL particles
Pattern or phenotype B refers to predominantly smaller, dense LDL particles

Estimating Lipoproteins Using Lipid measurements

TC represents the cholesterol content within all of the lipoproteins (dump trucks) that exists in a deciliter (dL) of plasma. Since the beta-lipoproteins are considerably larger than the alpha-lipoproteins approximately 75% of total cholesterol is carried in the apoB-containing particles, making TC an apoB surrogate (a TC > 200 should raise the suspicion of elevated apoB). VLDL-C, an often ignored lipid concentration, is not a measured lipid concentration but rather is calculated using the Friedewald formula, by dividing TG by 5. This calculation assumes, often erroneously as TG levels rise, that all TGs are in VLDL particles and that VLDL composition necessarily contains five times more TG than cholesterol molecules. Since a desirable TG is < 150 mg/dL, a normal VLDL-C is 150/5 or < 30 mg/dL (the higher the TG, the higher the VLDL-C). Although VLDL-C is at best a weak apoB surrogate,[14] data from the Framingham Heart Study showed that when both are added into the statistical model, VLDL-C is as good a predictor of CV risk as is LDL-C.[17] However, since the vast majority of the beta-lipoproteins are LDLs, LDL-C (especially if elevated) is a better apoB surrogate and is the primary CVD risk factor and goal of therapy in every guideline prior to 2008. LDL-C is usually calculated using the formula: LDL-C = TC minus (HDL-C plus VLDL-C). Upon special order, laboratories can directly measure LDL-C and this is most useful when TG levels are high which renders the Friedewald formula less accurate.[18] [Table 3].

TABLE 3 LIPID CONCENTRATION DETERMINANTS

TC = apoA-I-C + apoB-C
TC = HDL-C + LDL-C + VLDL-C + IDL-C + Chylomicron-C + Lp(a)-C + Remnant-C

Under normal circumstances, when fasting, there should not be any chylomicrons, remnants (smaller chylomicrons or VLDL particles) or very many if any IDL particles (these are postprandial lipoproteins). Most patients do not have Lp(a) pathology. Thus the lipid concentration formula simplifies:

  TC = HDL-C + LDL-C + VLDL-C
  VLDL-C is estimated by TG/5 (assumes all TG are in VLDLs and VLDL TG/Chol composition is 5:1)
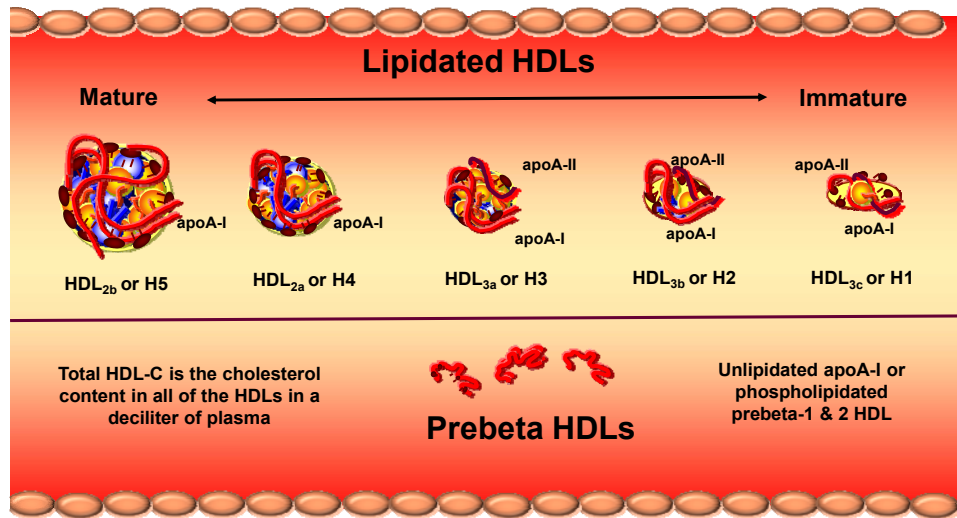 TC = HDL-C + LDL-C + TG/5
  LDL-C = TC – [HDL-C + TG/5]
  Non HDL-C = TC – HDL-C

In actuality, the calculated or directly measured LDL-C values in the standard lipid panel, represents LDL-C + IDL-C + Lp(a)-C. However, because labs do not usually separate IDLs and Lp(a) particles from LDLs (without significant added expense), only total LDL-C is reported.

The epidemiological data indicates that both HDL-C and apoA-I are strongly and inversely related to CVD risk in men and women suggesting HDLs may have cardioprotective abilities.[4] HDL particles are a heterogeneous collection of unlipidated apoA-I proteins, very small prebeta HDLs and more mature, lipidated HDL_3 and HDL_2 species (HDL_3 smaller than HDL_2). NMR nomenclature identifies the smaller HDL species as H1 & H2 and the larger HDL species as H4 & 5.[13] [Figure 4] Although HDLs can acquire cholesterol from any cell, including arterial wall foam cells, the majority of HDL lipidation occurs in the liver and proximal small intestine after which it is trafficked to steroidogenic tissue, adipocytes and ultimately back to the liver. Normally HDLs carry little TG.[19] HDL-C or the cholesterol content within HDLs is a surrogate of apoA-I or HDL-P, where the assumption is that higher HDL-C indicates higher apoA-I and vice versa. However the correlation between apoA-I and HDL-C varies, as each HDL particle can have from two to four apoA-I molecules and the volume of cholesterol within the particle is also a function of the particle size and its TG content. Total HDL-C for the most part is indicative of the cholesterol carried in the larger, mature HDL_2 (H4,H5) particles and patients with low HDL-C typically lack these mature, lipidated HDL particles. Since HDLs rapidly and repeatedly remodel (lipidate and then delipidate) over their 6 day half life, there is no predictable relationship between the total HDL-C level and the dynamic process termed reverse cholesterol transport. Neither HDL-C, nor apoA-I, nor HDL-P, nor HDL size are consistently related to HDL particle functionality, i.e. HDLs ability to lipidate or delipidate, appropriately traffic cholesterol or perform other non-lipid antiatherogenic functions.[19,20]

Figure 4

<table>
<tr><td colspan="6">Lipidated HDLs</td></tr>
<tr><td>Mature</td><td></td><td></td><td></td><td></td><td>Immature</td></tr>
<tr><td></td><td></td><td>apoA-II</td><td>apoA-II</td><td>apoA-II</td><td></td></tr>
<tr><td>apoA-I</td><td>apoA-I</td><td>apoA-I</td><td>apoA-I</td><td>apoA-I</td><td></td></tr>
<tr><td>HDL_{2b} or H5</td><td>HDL_{2a} or H4</td><td>HDL_{3a} or H3</td><td>HDL_{3b} or H2</td><td>HDL_{3c} or H1</td><td></td></tr>
</table>

Mature ← **Lipidated HDLs** → **Immature**

apoA-II, apoA-I

HDL_{2b} or H5　　HDL_{2a} or H4　　HDL_{3a} or H3　　HDL_{3b} or H2　　HDL_{3c} or H1

Total HDL-C is the cholesterol content in all of the HDLs in a deciliter of plasma

Prebeta HDLs

Unlipidated apoA-I or phospholipidated prebeta-1 & 2 HDL

HDLs which have a half-life of 6 days, originate in the liver or small intestine as secreted, unlipidated apoA-I or prebeta species which rapidly acquire cholesterol from hepatocytes, enterocytes, peripheral cells and arterial macrophages or from apoB particles (mediated by CETP) resulting in more mature, lipidated HDL species. The lipidated HDL traffics cholesterol to steroidogenic tissues, adipocytes and then ultimately in a complex process classically called reverse cholesterol transport (RCT), returns unused cholesterol to the liver or small intestine (<u>direct</u> RCT) or by transferring the cholesterol to apoB particles which traffic it to the liver (<u>indirect</u> RCT).

To most accurately predict lipid-related CVD risk, a clinician must determine which patients have elevated numbers of atherogenic lipoproteins using actual particle concentrations. In clinical practice lipoprotein particle numbers are best estimated, by scrutinizing all of the lipid concentrations and ratios (not simply LDL-C). TC and especially LDL-C are apoB and LDL-P surrogates, but the best lipid concentration correlate of apoB is the calculated non-HDL-C value. By subtracting HDL-C from TC, one identifies the cholesterol that is not in the HDL particles but rather in. all of the potentially atherogenic apoB particles. [Table 4] [Figure 5] In essence, non-HDL-C is VLDL-C plus LDL-C and is thus a better apoB or LDL-P proxy as compared to LDL-C.[17] If a patient is at LDL-C goal, but still has a high non-HDL-C, one can assume there are still too many apoB particles likely contributing to residual risk.

Since LDLs are the predominant apoB species, non-HDL-C is in actuality the best lipid concentration predictor of LDL-P.[14] Because neither the TC nor HDL-C assays require a patient to fast, non-HDL-C is accurate in non-fasting patients, making it a very practical way to screen for CVD risk.[6] In the Women's Health Study of mostly healthy women, non-HDL-C predicted CHD risk as well as did apoB but not as well as LDL-P.[21,22] In independent, separately published analyses from the Framingham Offspring Study, LDL-P was a better predictor of risk than was LDL-C or non-HDL-C[14] whereas apoB was no better than the TC/HDL-C ratio. [23]

Figure 5
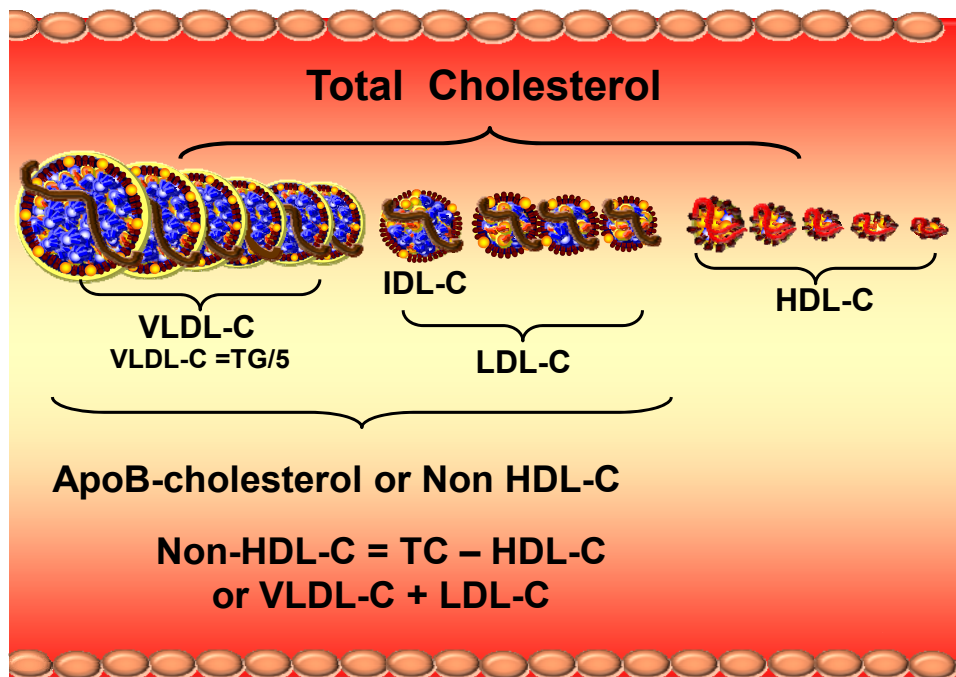
Non-HDL-C is calculated by subtracting HDL-C from TC and requires no fasting because LDLs and HDLs are in a steady state with half-life's of 3 days and 6 days respectively. Since a desirable VLDL-C is 30 mg/dL or less, the non HDL-C goal is the LDL-C goal (100 or 70 mg/dL depending on risk) plus 30 mg/dL (130 or 100 mg/dL). Non-HDL-C is in essence VLDL-C plus LDL-C. Patients with elevated TG have elevated VLDL-C (TG/5) often associated with low HDL-C and unremarkable LDL-C. Despite the latter, the non-HDL-C will be high unveiling how risk can be present even when LDL-C is normal, a common scenario in women. [27]

TABLE 4 Lipid Concentration Surrogates of Abnormal Lipoprotein Concentrations

Abnormal Apo B or LDL-P Lipid surrogates

TC ≥ 200 mg/dL
LDL-C ≥ 100 mg dL
Non-HDL-C ≥ 130 mg/dL

Very High Risk Patients
LDL-C ≥ 70 mg dL
Non-HDL-C ≥ 100 mg/dL

**Abnormal Apo A-I and HDL-P Lipid surrogates**

HDL-C < 50 mg/dL

Abnormal ApoB/A-I Lipid surrogates

TC/HDL-C ≥ 4.0
Elevated Non-HDL-C & low HDL-C in the face of a normal LDL-C

NCEP ATP-III guidelines introduced non-HDL-C as a secondary goal of therapy in patients with TG > 200 mg/dL. Subsequent data has shown that non-HDL-C is always a better predictor of risk than is LDL-C regardless of TG levels.[17] The AHA Women's Guideline was the first to set a desired non-HDL-C level (130 mg/dL) regardless of the TG value.[9] Since a normal VLDL-C concentration is 30 mg/dL, the non-HDL-C goal is 30 mg/dL above the desired LDL-C goal. For example, if the desired LDL-C is 100 mg/dL, the non HDL-C goal is 130 mg/dL. If the desired LDL-C goal is 70 mg/dL, as in a very high risk patient, the non-HDL-C goal would be 70 + 30 or 100 mg/dL.[9,11] It is unfortunate that despite the recommendations of guidelines, the vast majority of clinicians do not calculate or chart non-HDL-C or use it as a goal of therapy. For population cut points and desirable goals of therapy for lipid and lipoprotein concentrations see Figure 6.

Figure 6

Population Percentile Cut Points & Goals for LDL-C, Non-HDL-C, ApoB & LDL-P
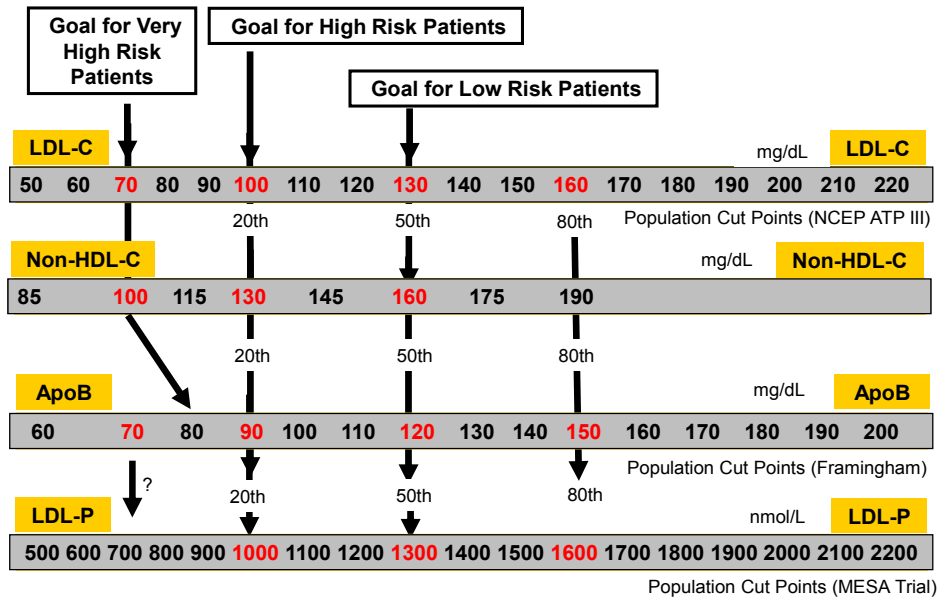

Population cut points are the % of the population that has a value above or below the percentile looked at in epidemiological trials; i.e. 50% of people have an LDL-C < 130 mg/dL, a non-HDL-C < 160 mg/dL, apoB < 120 mg/dL and LDL-P < 1300.

Lipoprotein Pathology:

The ability to predict lipoprotein particle concentrations using the lipid profile becomes far less accurate in those with cardiometabolic risk, defined as pathological states seen in insulin resistant and metabolic syndrome patients defined by elevations of TG > 150 mg/dL and reductions in HDL-C < 50 mg/dL in women with borderline or normal LDL-C levels. This has also been termed TG/HDL axis disorders [24] As TGs begin to rise above 120 mg/dL there is an increased hepatic secretion of apoB-containing TG-rich VLDL particles. As the VLDL-TG are hydrolyzed to fatty acids by lipoprotein lipase in muscle and fat cells, in a process termed lipolysis, the VLDL shrinks and transforms into IDLs. Ultimately, unless cleared by hepatic LDL receptors, the IDLs undergo additional lipolysis by hepatic lipase (HL) and transform into LDL particles which because of their longer half life accumulate, further raising apoB and LDL-P. As TG levels rise above 100-150 mg/dL, a lipid transfer protein

called cholesteryl ester transfer protein (CETP), exchanges the TG in VLDLs and chylomicrons for cholesteryl esters in LDLs and HDLs. This swap of TG for CE (from VLDL to LDL and HDL dump trucks) creates LDLs and HDLs that are TG-rich and cholesterol-poor, enabling additional TG removal by HL to create smaller LDL and HDL particles. The latter are so small, that surface apoA-I breaks loose and passes through renal glomeruli to be excreted, leading to reductions of apoA-I, HDL-P and HDL-C. Also created in this process are smaller, atherogenic cholesterol-rich VLDL and chylomicron particles termed remnants, diagnosable by an elevated VLDL-C. In essence the high TG elevates risk by creating too many atherogenic apoB dump trucks (VLDL remnants and small LDL). Such patients are said to have cardiometabolic risk and typically have elevated TG, reduced HDL-C, variable (but often unremarkable) LDL-C as well as increased TG/HDL-C ratios greater than 3.8 which is highly indicative of too many small LDLs (high apoB) and reduced numbers of HDLs (high apoB/A-I ratio). [7,25,26] [Figure 7]

Figure 7
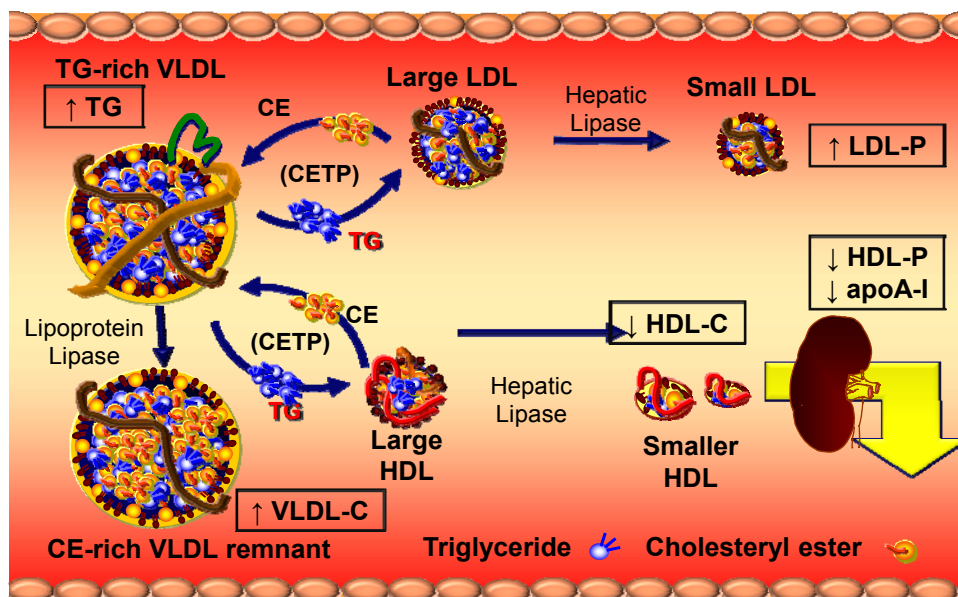
TG-rich lipoproteins, using CETP, swap TG for CE molecules leading to TG-rich & CE-poor LDL and HDL and TG-poor & CE-rich VLDLs. This leads to reductions in LDL-C and HDL-C and elevations in VLDL-C and non-HDL-C. The TG-rich & CE-poor LDL and HDL upon exposure to hepatic lipase lose TG and surface phospholipids and become smaller LDL and HDL particles. The latter are excreted by the kidneys leading to reductions in HDL particles and HDL-C. Characteristically such patients have high apoB (LDL-P), low Apo-A-I (HDL-P). Until proven otherwise patients with low HDL-C should be assumed to have too many LDL particles (elevated apoB & LDL-P).

Such a scenario, typical of TG/HDL axis disorders, explains much of the risk associated with rising TG levels and is very common in premenopausal women with insulin resistant states such as type 2 diabetes (T2DM) or polycystic ovarian syndrome or menopausal women with metabolic syndrome, T2DM or CHD. In the Framingham Heart Study, 80% of the enrolled women had a baseline LDL-C < 140 mg/dL and thus never would have qualified for any of the classic primary prevention therapeutic trials. Startlingly two thirds of the women, who experienced a coronary heart disease event over a twelve year period, had an LDL-C < 140 mg/dL and thus their CV risk would be missed if one was only looking at LDL-C. The most common lipid abnormality associated among those who had events was isolated elevation of TG (200 mg/dL or higher) or elevated TG and low HDL-C. [27] Risk in women and many men would be more evident if clinicians therefore also looked at TG, low HDL-C, TG/HDL-C, TC/HDL-C and especially non-HDL-C. Direct measuring apoB or LDL-P would eliminate the lipid concentration guesswork. [7]

Since spherical lipoprotein volumes are a function of the third power of its radius ($V=4/3\pi r^3$), patients with small LDLs will require up to 40-70% more LDL particles to traffic a given amount of LDL-C. [13] In such patients there is often little correlation (termed a disconnect) between LDL-C and LDL-P or apoB values: regardless of the LDL-C, the apoB, LDL-P or non-HDL-C is often elevated. [28] It takes many more small than large dump truck to carry a given load of cholesterol. Such risk cannot be predicted by looking only at LDL-C, which is the main reason guidelines advocate the use of non-HDL-C, TC/HDL-C ratio or apoB. [6,7,10] In summary, a large part of the risk seen in patients with low HDL-C (< 50 mg/dL) or high TG (>130-150 mg/dl) is the accompanying increased numbers of apoB particles (mostly small LDLs, but also increased numbers of remnant particles). [14,20,28] This is a crucial point and explains why treatment of low HDL-C states should always be directed first at reducing apoB or LDL-P (LDL-C and non-HDL-C), rather than raising apoA-I or HDL-C or lowering TG per se (Table 5 and 6). [6,8]

To illustrate the pathology described above, consider two different patients outlined in the case scenario table. Both patients 1 and 2 have the exact same, desirable TC and LDL-C values. However further analysis reveals an elevated TG and abnormal TC/HDL-C ratio and/or non-HDL-C in patient 2, indicative of higher risk for CVD. The TG/HDL-C ratio > 3.8 in patient 2 is highly suggestive of small LDL phenotype B and thus patient 2 will have somewhere between 40-70% more LDL particles to traffic her LDL-C as compared to patient 1 who probably has normal sized LDLs.[28] The elevated VLDL-C of patient 2 indicates the presence of VLDL remnants which predict risk above that conveyed by LDL-C.[6] The casual clinician looking only at TC or LDL-C would miss the increased risk (high apoB) in patient 2. Patient 2 needs significantly more apoB dump trucks as patient 1to traffic the 100 mg of cholesterol. Obvious clues to her lipoprotein pathology are the elevated TG and reduced HDL-C (TG/HDL axis disorder). Beyond elevated TG and reduced HDL-C, patient 2, with cardiometabolic risk, is also likely to have an increased waist size, subtle hypertension or even impaired fasting glucose which are the three additional parameters of the metabolic syndrome.[6,10,25]

Case Scenarios demonstrating disconnect between LDL-C and CV risk: (values in mg/dL)			
Patient 1		**Patient 2**	
Total Cholesterol	180	Total Cholesterol	180
LDL-C	100	LDL-C	100
HDL-C	60	HDL-C	40
VLDL-C	20	VLDL-C	40
TG	100	TG	200
Non HDL-C	120	Non HDL-C	160
TC/HDL-C	3.0	TC/HDL-C	4.5
TG/HDL-C	1.6	TG/HDL-C	5.0

SUMMARY: The major driving forces of atherogenesis are increased numbers of apoB-containing lipoproteins and impaired endothelial integrity. ApoB and LDL-P are the available lab assays that most accurately quantitate atherogenic particle number and they are now part of newer guidelines.[7] The lipid concentration surrogates clinicians should be using to more accurately predict apoB and CVD risk in addition to TC (unless HDL-C is very high), and LDL-C, are 1) Non-HDL-C, 2) TC/HDL-C and 3) TG/HDL-C ratios. Since LDLs are by far the most numerous apoB particles present in plasma, they are the primary agents of atherogenesis. ApoB and LDL-P do not correlate with LDL-C in patients who have cholesterol-depleted LDL particles, which are usually those with either small LDLs, or TG-rich and cholesterol-poor LDLs.[5,14] Refer to the simple algorithm in Table 7 to rapidly read a lipid profile and concisely predict lipid-related CVD risk or response to therapy.

Both NCEP ATP-III and AHA Women's Guidelines use the TC/HDL-C as a powerful risk predictor, but as a goal of therapy advise normalizing LDL-C and then

Non HDL-C.[6,10] In reality, if one normalizes the non-HDL-C, de facto the LDL-C will also likely be normalized. Example: when evaluating or treating a woman with an LDL-C of <100 mg/dL, but who has a non-HDL-C > 130 mg/dL or TC/HDL-C ratio > 4.0 the clinician should recognize that residual risk exists and elevated numbers of apoB particles are likely present. Therapy to normalize the non-HDL-C, or better yet the apoB (LDL-P) is warranted. The giveaways that residual risk is present when LDL-C is normal are reductions in HDL-C and elevations of TG and non-HDL-C and of course elevated apoB (LDL-P). It all comes down to accurately counting or estimating dump truck numbers.

Table 7   RAPID ANALYSIS OF THE LIPID PROFILE

1) Look at the TG: If > 500 mg/dL treatment is needed and the TG reduction takes precedence over all other lipid concentrations. If TG is less than 500 mg/dL, go to step (2).

2) Look at the LDL-C; if it is above 130 mg/dL risk is present and if >190 mg/dL, drug therapy is indicated regardless of other findings. At lesser levels, the need for therapy is based on the overall CVD risk of the patient. Therapeutic lifestyle recommendations are always indicated.

3) Look at the HDL-C: increased risk is present if < 50 mg/dL woman. Do not assume high HDL-C always means low CVD risk as upwards of 20% of women with CHD have HDL-C > 60 mg/dL.

4) Calculate the TC/HDL-C ratio: Increased risk is present if > 4.0 (a surrogate of apoB/apoA-I ratio).

5) Calculate the non-HDL-C (TC minus HDL-C). Newer data shows this calculation is always equal to or better than LDL-C in predicting CV risk. Non-HDL-C is less valuable if TG >500 mg/dL.

6) Calculate the TG/HDL-C ratio to estimate LDL size (80% chance of small LDL size if ratio > 3.8).

7) Look at VLDL-C (TG/5): If > 30-40 mg/dL remnant lipoproteins are present.

In closing, if used in its entirety, the lipid profile provides a significant amount of information as to the presence or absence of pathological lipoprotein concentrations (dump trucks). Far too many clinicians solely focus on LDL-C and do not use the rest of the profile estimate particle number. This shortcoming is a contributing reason why patients in the Framingham Study, especially women, have clinical events with elevations of TG, reductions in HDL-C and unremarkable LDL-C.[27] A solid understanding of the points elaborated in this article underscores how necessary both lifestyle and aggressive lipid-modulating drug therapy will be to achieve goals as set forth in AHA Women's and ADA/ACC guidelines. Therapeutically, it is much more difficult to reduce apoB than LDL-C or non-HDL-C.[29] Using apoB or LDL-P greatly simplifies risk assessment and treatment, as it is a single number, does not require fasting and takes away the confusion of estimating risk using borderline lipid concentrations. The most recent guideline from the ADA and ACC has now initiated the focus away from lipid concentrations and onto atherogenic particle concentrations, apoB and LDL-P.[7]

TABLE 4 ADA/ACC Consensus Statement on Lipoprotein Management

Measurments of choesterol are indirect estimates of lipoproteins transporting cholesterol

Routine use of non-HDL-C consitute a better index than LDL-C for identifying high risk patients

For patients with cadiometabolic risk (high TG, low HDL-C) measurement of apoB is warranted in those on pharmacologic treatment and apoB goals should be reached

LDL-P as measured by NMR is equally informative as apoB

Goals of therapy: apoB or LDL-P is the most important
High risk patients: LDL-C < 100 mg/dL   Non HDL-C < 130 mg/dL   ApoB < 90 mg/dL
Highest risk patients: LDL-C < 70 mg/dL   Non HDL-C < 100 mg/dL   ApoB < 80 mg/dL

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