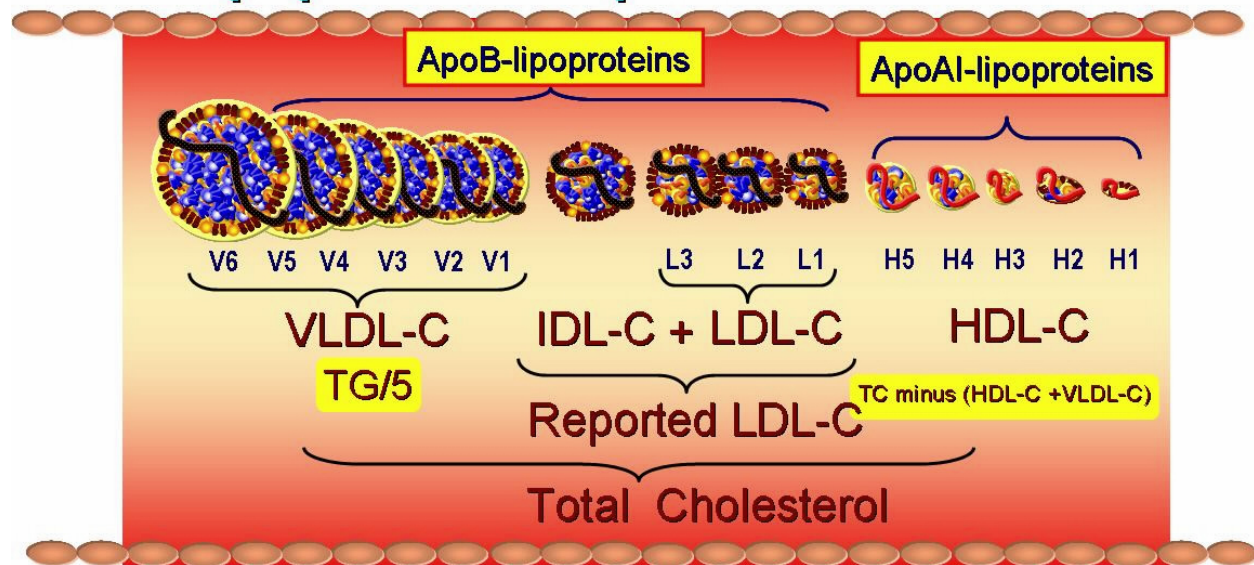


To my lipid friends: Permit me some sentiment. As a Memorial Day Tribute to all of those who have devoted service, bodies or supreme sacrifice in defense of our great country I offer tremendous gratitude and perpetual thanks. Especially fitting this year is the long over-due dedication of the WWII monument: I wish my Dad (a WWII vet) and my Mom (an aircraft engine assembler) were still alive to experience this belated National Thank You. He and millions like him and her came home, never mentioned the War again, never asked for thanks or anything else, never sued anyone, never moaned, and simply went about working their butts off making America the great country it is. Indeed: they are/were the greatest generation! Those of us that followed have a lot to live up to.

Now to my on-going discussion of lipid basics:

Lipoprotein & Lipid Concentrations



The above diagram nicely depicts the relationship of lipids and lipoproteins. In the diagram, blue represents triglycerides, yellow is cholesterol. The bars across the lipoproteins represent surface apolipoproteins, namely apoB (brown) and apoA (red). Note there is one apoB on each beta-lipoprotein. Please realize that when you try to ascertain CV risk using a lipid profile, you are using lipid values as surrogates or "proxies" of lipoproteins.

There are two types of lipoproteins alpha and beta, based on electrophoretic motility. The apoB particles are potentially atherogenic, the apoA are not. Apolipoprotein B (apoB) levels quantitate all of the beta-lipoproteins per dL of plasma. The beta family consists of VLDL, IDL, and LDL. Also included (if present) are lipoprotein (a), chylomicrons and remnant lipoproteins. NMR LipoProfiles quantitate each of the beta-lipoproteins subclasses.

Note that all of the major lipoprotein classes have subclasses based on size and lipid/protein and phospholipid concentrations. Using NMR technology there are 6 VLDLs, three LDLs and five HDLs. They are numbered from smallest (1) to largest (6). All persons have each of the particles but with respect to LDLs each of us has a predominant species called pattern or phenotype: large (A) or small (B). The A and B labels have nothing to do with the surface apolipoproteins A or B.

Total cholesterol is the cholesterol content of every lipoprotein that exists in a dL of plasma. It does not require fasting as most of the cholesterol is carried in LDL and HDL particles and those particles have half-lives of 3 and 5 days respectively and exist in a steady state.

HDL cholesterol or HDL-C is the cholesterol content of all of the HDL particles (big and small) in a dL of plasma. ApoA1 would be an indicator of HDL particle concentration. HDL-C does not require fasting because of the long half-life of HDL particles. HDL-C levels do not necessarily reflect reverse cholesterol transport or flux, as both big and small HDL particles are in dynamic flux. In general, with genetic exceptions to the rule, increased levels of HDL-C are desirable and decreased levels are associated with significant CV risk.

VLDL cholesterol or VLDL-C is the cholesterol content of all of the VLDL particles (including remnants) in a dL of plasma. Since it is a TG-rich lipoprotein with a half-life of 6 hours VLDL-C measurement does require fasting. The value reported on the lipid profile report is calculated by dividing one's TG value by 5. This formula assumes all of the TG molecules exist in VLDL particles and that the ratio of TG to cholesterol within the VLDL particle is 80 to 20% or 5 to 1. Both of those assumptions are incorrect as a patient's TG level rises above 200 mg/dL. So one should not put much reliance on a calculated VLDL-C in a patient with a TG > 200 mg/dL.

With respect to VLDL subparticles, the larger V5 and V6 represent atherogenic chylomicron remnants: chylomicrons of reduced sized due to partial lipolysis (TG removal). Large VLDLs also are likely, through further lipolysis, to become small LDL. The smaller VLDL (V1 and V2) are atherogenic VLDL remnants. Thus, if present in increased amounts, all VLDL are potentially atherogenic particles.

IDL cholesterol is the cholesterol within the IDL particles in a dL of blood. IDL-C is never reported in a lipid profile, but rather incorporated into LDL-C values. All IDL particles are highly atherogenic particles. They have a very transient half-life. They undergo rapid lipolysis and become LDL particles. If they are TG-rich and cholesterol poor, they become small LDL particles. Advanced lipoprotein testing is required to quantitate IDL concentrations.

LDL cholesterol or LDL-C semantically represents the cholesterol within all of the LDL particles in a dL of plasma. However, the value reported in most lipid profiles actually represents the cholesterol in both LDL and IDL particles. LDL-C from most laboratories is usually is not measured but rather estimated using the Friedewald formula:

$$\text{LDL-C} = \text{total cholesterol} - \text{HDL-C} + \text{VLDL-C} \quad \text{or} \\ \text{LDL-C} = \text{TC} - [\text{HDL-C} + \text{TG}/5]$$

Since the Friedewald calculation is based on a calculation which includes TG, the patient has to be fasting > 12 hours. As mentioned above, the equation loses accuracy as TG levels exceed 200 mg/dL.

However, if requested a lab will measure LDL-C directly. Direct LDL-C measurements do not require fasting. If present in increased numbers, LDL particles are the most atherogenic of all lipoproteins and impart CV risk. LDL particles have a half-life of three days. When you base CV risk using LDL-C values, as per the NCEP guidelines, you are simply using LDL-C as a surrogate or proxy of apoB. If one measures apoB, 90% of apoB concentrations represent LDL particles: as LDL particles have much longer half-lives than VLDL and other apoB particles.

Non HDL-C is a better surrogate for apoB in patients with elevated TG and the Non HDL-C calculation does not require fasting:

$$\text{Non HDL-C} = \text{Total cholesterol} - \text{HDL-C} \\ \text{Non HDL-C is in effect LDL-C} + \text{IDL-C} + \text{LDL-C} + \text{Remnant-C} + \text{Lp(a)-C}$$

Useful lipid and apolipoprotein Ratios:

ApoB/ApoA1 Ratio of atherogenic to non-atherogenic particles
TC/HDL-C Ratio of atherogenic to non-atherogenic cholesterol
LDL-C/HDL-C Ratio of atherogenic to non-atherogenic cholesterol
LDL-C/ApoB indicator of LDL particle size:

If > 1.0 particles are large: If < 1.0 particles are small
TG/HDL-C Indicator of LDL size: If > 3.0 LDL particles are small

If you are using lipids instead of lipoproteins in doing CV risk: you assume the following:

Increased TC = Increased amounts of apoB lipoproteins (could be VLDL and/or LDL)
Increased LDL-C = Increased amounts of apoB lipoproteins (most LDL particles)
Normal or low LDL-C = normal amounts of LDL particles and apoB
Elevated TG = increased amounts of VLDL, VLDL or chylomicron remnants and apoB
Elevated TG = increased amounts of small LDL and apoB
Reduced HDL-C = increased amounts of VLDL remnants and small LDL: increased apoB

Elevated TG and reduced HDL-C are major components of the metabolic syndrome. LDL-C is usually normal or minimally elevated in the metabolic syndrome due to the predominance of small LDL.

In clinical and epidemiological trials, lipid measurements are not as accurate as apoB or apoA. In the Women's Health Study, NMR measurements out predicted apoB. From the great primary prevention trial AFCAPs-TexCAPS: quoting from the study conclusion:

It is well documented by many observational studies, including most recently the Quebec Cardiovascular Study, that apoB is a more powerful independent predictor of CHD than LDL-C. Although apoB is associated with known atherogenic lipoprotein species, such as IDL remnants and small, dense LDL (a distinct, highly atherogenic subpopulation), LDL has a variable cholesterol content. This variability in the composition of LDL has been hypothesized to explain the clinically observed variation in risk that appears to be independent of LDL-C. Our results suggest that it may be more valid to use apoB rather than LDL-C to assess the on-treatment effect of reducing the atherogenic burden, especially when LDL-C is not markedly elevated. In the present analysis, the use of the apoB/AI ratio, which takes into consideration most, if not all, of the beneficial changes in lipoprotein metabolism produced by statins, provides a remarkable continuum of risk, with no apparent threshold to benefit. Furthermore, in the last few years, the measurement of apos B and AI has become more widely available, lower in cost, and, because of international efforts, more standardized. These results suggest that reconsideration should be given to apos B and AI in risk assessment and that treatment goals based on apoB and/or the apoB/AI ratio be further explored in certain populations. (Circulation. 2000;101:477-484.)

Best regards, Tom

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