SJHG Heartbeat

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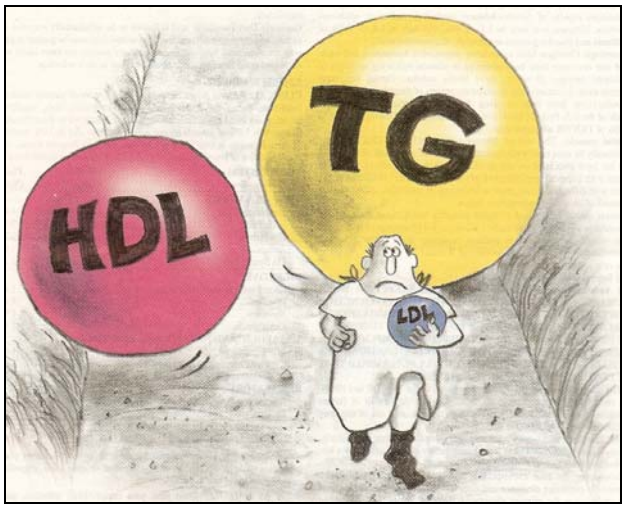
Paradigm Shift To More Reliable Lipid Risk Stratification

High TG and low HDL-C



This *Heartbeat* will focus on the importance of mixed dyslipidemia and its associated high risk for coronary heart disease (CHD) events. In particular, TG/HDL axis disorders (common in diabetes [T2DM] and metabolic syndrome [MetS]), characterized by the triad of a high level of triglycerides TG), a low level of high-density lipoprotein cholesterol (HDL-C) and increased concentrations of atherogenic small, dense low-density lipoprotein (LDL) particles (increased apoB or LDL-P), confer a high risk of CHD events. This risk is frequently still present when the common standard of measuring lipid risk, low-density lipoprotein cholesterol (LDL-C) is at or near normal range without treatment and in many cases at optimal goal (< 70mg/dL) on statin therapy. We will review two trials that illustrate this. In addition we will present rationale to justify a *paradigm shift* in how we should identify and treat lipid risk.

Low HDL-C: In the post hoc analysis of the Treating to New Targets (TNT) trial data of 9700 patients, low HDL-C levels predicted increased CV events in patients with very low LDL levels.[1] The initial TNT trial (comparing effects of atorvastatin 10mg with 80mg) was one of several studies that made the "lower-is-better" case for lowering LDL-C beyond the then-current recommended guidelines.[2] TNT showed that lowering LDL-C levels in stable CAD patients substantially below the current guideline target of < 100mg/dL was beneficial.

In the post hoc analysis of TNT, a total of 9770 study patients ages 35 to 75 with clinically evident CAD were stratified by quintile of HDL-C level at 3 months of statin treatment. In multivariable analysis, this HDL-C quintile was a strong and significant predictor of CV events. Patients in the lowest quintile (< 38mg/dL) had a 25% higher risk for CV events than those in the highest quintile (≥ 55mg/dL). This relationship was independent of statin dose or LDL.

The post hoc TNT study is important because it identifies low HDL-C's association with residual risk in patients who have reached their 'lower is better' LDL-C target goal. Secondly, it indirectly emphasizes the importance of NCEP ATP-III secondary goal or target, non-HDL-C, especially in situations where the particles transporting the cholesterol are likely small, dense LDL particles which cannot be identified by an LDL-C level. There is obvious risk in these patients, since those with low HDL-C also have associated higher incidence of elevated TG and apoB (LDL-P) along with lower levels of apoA-I (a surrogate of HDL particle concentration).

Non-HDL-C, which was unfortunately not addressed in the study, is the secondary goal of therapy per

NCEP ATP III Guidelines when TG is > 200mg/dL. There is emerging consensus on the position that non-HDL-C is a better lipid surrogate than LDL-C, even when TG is in normal range. This is especially true with low HDL-C or high TG when LDL-C is just not a representative surrogate of the real risk (LDL-C disconnect). It can not be over-emphasized that both LDL-C and non-HDL-C are just surrogate goals of apoB (LDL-P)—the atherogenic particles which transport cholesterol into the vessel wall.

The authors also did not statistically adjust for apoB in their multivariate analysis. The statistically significant association with low HDL-C and residual risk was not present in those on atorvastatin 80mg (a powerful apoB lowering drug). It was only statistically positive in the combined group of atorvastatin 10mg and 80mg where apoB levels were higher.

High TG: In another post hoc analysis of a statin lipid-lowering study using the "lower is better" case, PROVE-IT, elevated TG (> 150mg/dL) was shown to significantly impact risk independent of LDL-C.[3] The original PROVE-IT trial of acute coronary syndrome (ACS) patients comparing pravastatin 40mg vs. atorvastatin 80mg revealed that the statin treatment which achieved the lowest LDL-C as well as lowest *hs*-CRP (high sensitivity or cardio C-reactive protein) had statistically significant improved outcomes.[4] Atorvastatin was more efficacious, although in those patients in which pravastatin reduced LDL-C < 70mg/dL and *hs*-CRP < 2.0, the benefits were equal, seeming to prove that getting to an appropriate goal is more important than which statin is used.

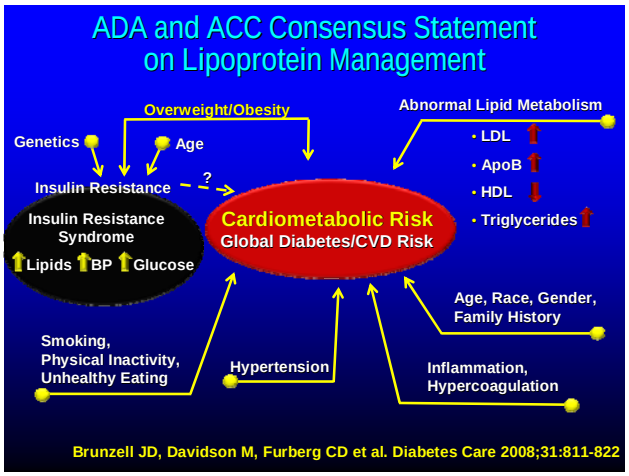
In the new subsequent analysis of PROVE-IT, the most noteworthy finding was the reduced CHD risk with low on-treatment TG (< 150mg/dL) that was independent of LDL-C. For each 10mg/dL decline in on-treatment TG, there was a 1.6% lower risk after adjustment for LDL-C. Elevated TG changes the composition of the HDL and LDL particles as well as the functionality of HDLs. The result is TG rich/ cholesterol poor smaller LDLs and much higher LDL-P concentrations.

Dr Thomas Dayspring in a Biocritique of this data comments, "It is unfortunate that the PROVE IT study did not quantitate LDL particle concentration using apoB or LDL-P." He believes that the high TG increases risk but primarily is a marker for increased LDL-P. "I think we then would have discovered much of the real risk attributable to the TG level." The investigators, however, did look at non HDL-C, the best lipid surrogate of apoB or LDL-P. It seems intuitive that by adding VLDL-C to LDL-C to give total "atherogenic cholesterol" (non-HDL-C), the risk from all the atherogenic particles would be accounted for more completely. As surmised, the patients with the lowest non-HDL-C levels had the least number of events. With respect to treatment efficacy, as TG levels fall below 150 mg, there is often a shift of LDL size to larger particles, which can be more easily removed by the statin upregulated LDL receptors. The authors suggest that this data may support the addition of fibrates or niacin to statin therapy to maximize TG reductions. On-going trials with combination therapies will answer this question.

Panel says apoB levels better than LDL-C

In a joint statement by the American Diabetes Association (ADA) and the American College of Cardiology (ACC), experts say, "Measuring LDL-C may no longer be the best measure of heart health in patients at high-risk for heart attacks and strokes."[5] According to the panel, after "LDL-C is lowered to recommended levels in high-risk patients, testing for the protein apoB or LDL-P may more accurately identify those still at risk for CHD events." This *consensus statement* is in the context of global cardiometobolic risk (CMR) which describes a clustering of risk factors (Fig.1) and a high-risk situation—discussed in our introduction. It is an attempt to address the considerable and persistent residual risk in many patients with adequate LDL-C lowering—especially those with CMR.

Figure 1. Factors contributing to metabolic risk.



Summary/Conclusions:

LDL-C at best is only our 3rd best surrogate for apoB behind LDL particle number (LDL-P) and then non-HDL-C.

The current practice described in TNT and PROVE-IT reflects the contrast between the robust and well-publicized clinical trial evidence for LDL-C-lowering therapy, contrasted with the fact that a direct measure of apoB (now readily available and standardized) or LDL-P are our best measures of atherogenic risk and are not to appropriate goal even though LDL-C may be < 70mg/dL. These measures are particularly important in high-risk CMR and ACS patients with persistently low HDL-C and/or high TG.

We would urge using non-HDL-C as your primary surrogate goal (30mg lower than the NCEP directed LDL-C goal) in all, but especially those with low HDL-C or TG > 100mg/dL.

Once at appropriate LDL-C goal or preferably non–HDL-C goal, check an apoB or LDL-P level and then target apoB or LDL-P based on consensus.

TREATMENT GOALS:	LDL-C	non-HDL-C	ApoB	LDL-P
Highest-risk patients				
• known CVD or • CMR plus one or more additional CVD risk factor	< 70	< 100	< 80	< 1000
High-risk patients				
• no CMR or known clinical CVD but 2 or more additional major CVD risk factors	< 100	< 130	< 90	< 1300
• CMR but no other CVD risk factors				

Treatment Plan:

Statins in conjunction with TLC are obviously first-line treatment for all at-risk patients. HDL-C is a marker for risk, but no treatment goals are presently indicated other than therapeutic lifestyle changes (TLC). Make sure that non-HDL-C is to appropriate goals. High TG is a marker for remnant lipoprotein and increased LDL-P. The proper way to treat TG is to inhibit their synthesis with TLC, fenofibrates, Niaspan or very high dose N-3 fatty acids.

If non-HDL-C is being driven by VLDL-C (TG):

- If diabetic and TG > 200 ►fenofibrate
- If no diabetes, TG < 200 and low HDL ►Niaspan
- If TG▲ > 500 ►fenofibrate + high dose N-3 fatty acids (4gm)

If non HDL-C is being driven by LDL-C, maximize statin and add ezetimibe or a bile acid sequestrant to the statin.

If non HDL-C is being driven by high LDL-C and VLDL-C despite the statin, add fenofibrate/or Niaspan, high dose N-3 FA and ezetimibe if needed.

- Non-HDL-C = TC - HDL-C or alternatively, LDL-C + VLDL-C (TG/5).
- LDL-C = TC – [HDL-C + VLDL-C (TG/5)] (Friedwalde equation). This can sometimes explain the LDL-C disconnect when TG is high.
- The ***NMR LipoProfile***® test, developed by LipoScience, Inc., is the only test that quantifies LDL particle number (LDL-P) using Nuclear Magnetic Resonance Spectroscopy.

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