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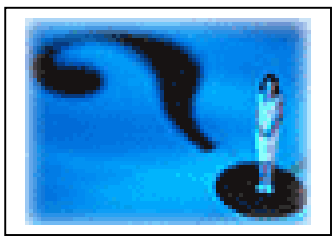
Beyond LDL-C: Where should our Focus Be?



The importance of statin therapy in reducing LDL-C levels and cardiovascular (CV) risk in both primary and secondary prevention is well established. Clinical-trial data have shown that reduction of LDL-C significantly reduces the incidence of coronary artery disease (CAD), decreases the occurrence of cardiac events, and slows atherosclerotic progression. Based on the most recent data with aggressive lipid-lowering therapy and goal LDL-C levels of < 70mg/dL, even more impressive 30% reductions in cardiovascular morbidity and mortality have been obtained.

What about the other 70%? A substantial number of individuals still experience cardiac events. This *Heartbeat* will discuss and analyze a just-released study which asks the question, "Does HDL still retain its strong prognostic value in patients with very low LDL levels?" We'll then present some options of how to proceed, looking at risk associated with high non-HDL, low HDL-C and high triglycerides.

For purposes of review before proceeding to the new material, we'll cover the present 'state of the art' of advanced lipid-lowering for secondary prevention based on updated NCEP ATP III Guidelines[1] and the secondary prevention guidelines from the AHA/ACC (Table 1)[2].

Table 1. LIPID MANAGEMENT

Goal LDL-C<100 mg/dL
If Triglycerides are > 200mg/dL,
Non-HDL should be < 130mg/dL.
[Non HDL-C = TC – HDL-C]

For all patients:
- Start dietary therapy. Reduce intake of saturated fats (to < 7% of total calories), *trans*-fatty acids and cholesterol (to < 200mg/d).
- Adding plant stanol/sterols (2g/d) and viscous fiber (>10 g/d) will further lower LDL-C.
- Promote daily physical activity and weight management.
- Encourage increased consumption of omega-3 fatty acids in the form of fish‡ or in capsule form (1g/d) for risk reduction.

For treatment of elevated triglycerides, higher doses are usually necessary for risk reduction.

For lipid management:
Assess fasting lipid profile in all patients, and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. For hospitalized patients, initiate lipid-lowering medication as recommended below before discharge according to the following schedule:
- LDL-C should be < 100 mg/dL
- Further reduction of LDL-C to < 70 mg/dL is reasonable.
- If baseline LDL-C is > 100 mg/dL, initiate LDL-lowering drug therapy.
- If on-treatment LDL-C is > 100 mg/dL, intensify LDL-lowering drug therapy (may require LDL lowering drug combination //).
- If baseline LDL-C is 70 to 100 mg/dL, it is reasonable to treat to LDL-C <70 mg/dL. (Non-HDL goal would be <100mg/dL)
- If triglycerides are 200 to 499 mg/dL; non-HDL-C should be < 130 mg/dL.
- Further reduction of non-HDL-C to < 100 mg/dL is reasonable.
- Therapeutic options to reduce non-HDL-C are:

(1) More intense LDL-C–lowering therapy, or
(2) Niacin (after LDL-C–lowering therapy), or
(3) Fibrate therapy# (after LDL-C–lowering therapy)

· If triglycerides are > 500 mg/dL#, therapeutic options to prevent pancreatitis are fibrates or niacin before LDL-lowering therapy; and treat LDL-C to goal after triglyceride-lowering therapy. Achieve non-HDL-C < 130 mg/dL if possible.

LDL-C Goal

LDL-C is purported to be one of the surrogates for ApoB (the lipoprotein transport vehicle that drives cholesterol into the vessel wall)—per National Cholesterol Education Program (NCEP)-Adult Treatment Program (ATP) III guidelines. (If ApoB is controlled it is unlikely that atherogenisis can occur.) According to ATP III, the LDL-C goal in high-risk patients is <100 mg/dL.

A recent update to ATP III listed a lower optional LDL-C goal of <70 mg/dL for very *high-risk* patients, including those with T2DM or MetS, tobacco dependence and CAD or acute coronary syndrome. The risk for cardiac events among these patients is essentially twice that of CAD without additional risk. Trials have suggested incremental risk reduction from LDL-C levels in the range of 70 mg/dL in both very-high-risk and stable CAD patients.[3] Cannon and colleagues believe that the guidelines should change the < 70mgdL goal from optional to recommended. For this reason, many lipid experts—*the 'lower is better' posse*—now consider intensifying lipid-lowering therapy to achieve even lower LDL-C levels (< 70mg/dL) in all patients with known CAD—but especially high-risk patients. The patient's entire lipid profile should be scrutinized, particularly non–HDL-C, before considering increasing the statin dose or going to combination lipid-lowering therapy.

Non–HDL-C Goal

Studies have shown that non–HDL-C is a better predictor of future CHD events than LDL-C. [4] In patients with high TG (> 130mg/dL) or low HDL-C (< 40mg/dL)—TG/HDL axis disorders (in whom LDL particles are small) and LDL-C is at or near normal—LDL-C is simply not as good a surrogate for ApoB as non-HDL-C. This is especially true in T2DM and MetS patients who have abnormalities of the TG/HDL-C axis. Because of this, ATP III designated non–HDL-C as a secondary target of therapy after LDL-C. This target is brought into play when TGs are ≥200 mg/dL. At lower TG levels, LDL-C is highly correlated with non–HDL-C levels. Even so, *non–HDLC may replace LDL-C as the primary target in all patients*. With the more aggressive therapy non-HDL-C (TC - HDL-C) goal is < 100mg/dL, 30mg/dL higher than the LDL-C goal. In summary, **reducing levels of non-HDL cholesterol is becoming an increasingly important target as the incidence of visceral obesity, T2DM, and MetS continues to escalate in the US.**

ATP III Risk Categories: LDL-C, Non-HDL-C Goals

Risk Category	LDL-C	Non-HDL-C
High: CHD or risk equivalent (10-yr risk > 20%)	< 100mg/dL Optional: **< 70mg/dL**	≤ 100mg/dL
Moderately High: 2+ risk factors or MetS (10-yr-risk 10-20%)	< 130mg/dL Optional: **< 100mg/dL**	≤ 130mg/dL

HDL-C Goal

According to ATP III, HDL-C is a tertiary target of therapy. A low HDL-C is < 40 mg/dL in men and < 50mg/dL in women. No treatment goals or modalities are mentioned. Although low HDL-C *as a marker* strongly associates with higher CAD risk, the mechanisms underlying this association are not well understood. Most of the risk associated with low HDL-C is due to elevated apoB (even if LDL-C is at goal) and decreased functionality of the HDL particles (inability to perform macrophage Reverse Cholesterol Transport (RCT) and deliver cardio-protective proteins to the plaque). Unfortunately, we have no way of measuring HDL functionality—a term coined by Dr Dan Rader (University of PA) in describing HDL particles delipidating cholesterol from arterial wall foam cells. Also, HDL functionality does not correlate with what a drug may or may not be doing to HDL-C levels. So we really have to concentrate our therapeutics on apoB or its surrogates—non-HDL-C and LDL-C.

While no benefits of treatment or elevating HDL-C have been demonstrated, it is known that HDL-C is inversely associated with non–HDL-C levels; thus, part of the association between low HDL-C and CAD almost certainly is confounded by a higher non–HDL-C. Although evidence from epidemiology and clinical trials clearly indicates that patients with lower HDL-C levels have more events than those with higher levels (even if on statins), we have no level-one trial evidence that proves the hypothesis that raising HDL-C is required once apoB or its surrogate (non-HDL-C) is at goal.

Does HDL Matter When Statins Are Working?

Little information is available about CV risk in patients who are treated aggressively with statins resulting in LDL-C levels < 70mg/dL. So, does a low HDL-C still matter? ***The answer appears to be yes***, according to a post hoc analysis of the Treating to New Targets (TNT) trial data of 9700 patients in which HDL-C levels predicted CV events in patients with very low LDL levels. [5]

The original TNT trial was one of several studies that made the "lower-is-better" case for lowering LDL cholesterol beyond the then-current recommended guidelines. TNT showed that lowering LDL-cholesterol levels in stable CAD patients substantially below the current guideline target of < 100mg/dL was beneficial. Atorvastatin 80mg reduced the primary composite end point of death from CHD, nonfatal MI, resuscitation after cardiac arrest, and fatal or nonfatal stroke by 22%, compared with patients treated with atorvastatin 10 mg. [6]

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

Commenting to *Heartwire* on the results of the study, **Dr Monty Krieger** (Massachusetts Institute of Technology, Cambridge, MA) said that this is yet another study showing that HDL-C is cardio-protective, this time at various LDL levels, and will reinforce the concept that doing something to treat low levels of HDL cholesterol may be beneficial, regardless of the LDL-C numbers.

Discussion

The post hoc analysis of the TNT study is important for two reasons. First, it identifies persistent risk when HDL-C is low in patients who have reached their 'lower is better' LDL-C target goal. Secondly, it indirectly emphasizes the importance of non-HDL-C as a secondary target of therapy, especially in situations where LDL-C are likely small, dense particles. There is obvious risk in these patients, since those with low HDL-C also have associated higher incidence of elevated TG and ApoB along with lower levels of ApoA (Table 1 in the study).

The lower HDL-C patients also had a higher incidence of tobacco dependence, T2DM and obesity and probably MetS (although waist circumference and insulin resistance were not measured—a limitation of the study). All of these factors are associated with higher risk which the low HDL-C identified. Strangely, no mention of non-HDL-C, the secondary goal of therapy is made—by the authors or Dr Krieger. **The authors also did not <u>statistically</u> 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 drug). It was only statistically positive in the**

combined group of atorvastatin 10mg and 80mg.

Based on the aforementioned association, and the probably coexisting TG/HDL-C axis disorders, many of these patients have small LDLs and have not reached their non-HDL-C (ApoB) goals. Since persistent risk with low HDL-C was identified when LDL-C goals (< 70mg/dL) were achieved, the next move would be to calculate the non-HDL-C goal (a more reliable surrogate in these patients) and get that to < 100mg/dL—30mg/dL higher than the LDL-C goal.

Therapeutic Options

Maximizing TLC (Therapeutic Lifestyle Changes), although difficult, must be a component of all risk reduction strategies. Tobacco cessation, weight reduction, and an appropriate exercise regimen are critical for improving everyone's risk profile. **The cornerstone in the management of non-HDL cholesterol always begins with TLC therapy, especially because robust reductions in TG levels may be achieved when combining dietary modification with an exercise regimen. In addition aerobic exercise and tobacco cessation can increase HDL-C 5-10%. Mild alcohol consumption (1-2) daily can increase HDL-C 5-15%.**

Intensifying statin therapy to further reduce LDL-C and non–HDL-C based on data from TNT, in which increasing atorvastatin from 10 to 80 mg produced a 25% further reduction in new coronary events.

After TLC, three options can be considered as "add-ons" to current statin therapy:

Adding a second LDL-C–lowering agent like ezetimibe 10mg, a cholesterol absorption inhibitor (a great add-on to any statin), to standard-dose statin therapy will lower LDL-C and non–HDL-C levels by around 25%, nearly the same as changing to a high-dose statin. A 16% reduction can be attained by adding a bile-acid sequestrant (e.g. colesevelam, 6 large capsules), which improves glucose control in patients with diabetes. Bile acid sequestrants should be avoided in patients with severe hypertriglyceridemia because of their tendency to raise TG levels.

Adding a fibrate, the drug of choice for high TG, can reduce CVD risk but, at best, only by about half that of statins. There are data supporting some benefit, but none showing that fibrates further reduce CVD risk with a statin. However, their favorable effects on lipoprotein metabolism make them an option—especially in those with T2DM or MetS. Fibrates lower LDL-C and non–HDL-C along with TG and increase HDL-C. Fibrates decrease small dense LDL in favor of larger, more buoyant LDL particles, which are less susceptible to oxidation and less atherogenic. Fenofibrates are the safer fibrate when used with statins because of significantly lower incidence of myopathy.

Adding niacin, the drug of choice to elevate HDL-C, has some evidence supporting risk reduction but only limited evidence of benefit with statin therapy. It can be combined with a statin in T2DM to decrease non-HDL-C presumably by producing a significant rise in HDL-C. It also decreases LDL-C and TG. Niacin therapy has been associated with slight rises in glucose, so sugars should be monitored.

Plan for patients in this study: When LDL-C is at goal (< 70mg/dL) and apoB (non HDL-C) is still abnormal, there are usually too many VLDL remnants and small LDLs in the plasma and these patients are not sufficiently treated. If statins have not normalized apoB (non HDL-C), then add fenofibrate, niacin or ezetimibe to get to appropriate goals. Ezetimibe would be the statin add-on if TGs are < 130mg/dL. However when TG is increased and HDL-C is low, LDLs are usually small. Then niacin or fibrates are a better choice as the statin add-on.

Some of these patients will need triple combination therapy to get to appropriate target goals. The strongest, well-tolerated, best triple

combo is rosuvastatin (Crestor) 40mg, ezetimibe (Zetia) 10mg and a fenofibrate (Tricor 145mg, Antara 130mg or Triglide 160mg).

Low HDL-C as a Treatment Target, by itself is not currently a treatment option. Without a firm understanding of how to favorably affect HDL functionality, and the paucity of CV outcomes data supporting increasing HDL-C, it shouldn't be a treatment goal. Beyond TLC, using combination therapy (statin +/- fibrate +/- niacin +/- ezetimibe) to reach non-HDL-C goals is encouraged. Both fibrates and niacin are proven to reduce events in patients with low HDL-C. Using them will complement statins lowering non-HDL-C, TG and apoB and maybe enhance HDL functionality as they increase HDL-C levels.

Summary/Conclusions

The current practice described in this analysis reflects the contrast between the robust and well-publicized clinical trial evidence for LDL-C-lowering therapy, contrasted with the more nebulous area of HDL-C-raising therapy. The lack of data supporting combination therapy, along with their cost and increased side effects, generally reflect our current general reluctance to treat low HDL-C. We have pushed the focus to look at the highly underutilized non-HDL-C (ApoB surrogate) goals and the utilization of combination therapy to get ApoB to goal levels with a statin as the foundation. It is unlikely that atherogenisis can occur if ApoB is controlled. HDL-C can be increased and/or TG decreased as a secondary effect of the particular chosen add-on therapy to statins—but with unproven benefit.

Given the high prevalence of low HDL-C and its substantial associated CV risk, development of more potent HDL-C-raising therapies or publication of more compelling evidence for current combination therapy has the potential to result in reduced CV morbidity and mortality especially in patients with T2DM or MetS.

Rather than risking patients' lives on NCEP ATP III lipid surrogates for ApoB—LDL-C and non-HDL-C, future emphasis may switch to more reliable risk stratification by routinely either directly measuring ApoB or obtaining an NMR Lipoprofile by LipoScience (locally through LabCorp) to determine LDL particle concentration (LDL-P) which shows the best correlation to ApoB[7]. Then treat the ApoB or LDL-P to appropriate goals.

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