Unfinished Business in CVD Risk Reduction

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Forgotten Majority

Although treatment with statins has reduced cholesterol levels and lowered cardiovascular disease (CVD) mortality rates approximately 30%, all the clinical studies have indicated that CV events continue to occur in the other 70%. Despite meaningful progress in the identification of risk factors and the development of highly effective clinical tools, deaths from CVD continue to rise worldwide. The obesity epidemic, metabolic syndrome (MetS) and the rising incidence of type 2 diabetes (T2DM) in our young and aging baby boomers have led to an upsurge in CVD.

This *Heartbeat* will characterize the increased CV risk associated with MetS and T2DM and discuss the efficacy of lifestyle changes, statins, fibrates and ezetimibe, by themselves and in combination, in treating patients with mixed dyslipidemia and T2DM or MetS.

Trojan horse

The past decade has seen a doubling in the national rate of obesity, which has contributed to a dramatic rise in the incidence of T2DM and MetS. Patients with T2DM or MetS have a 2- to 4 fold increase in their risk of CVD. This is happening while cholesterol levels in older Americans are dropping, most likely as a result of the increased use of statins.

Associated lipid abnormalities are the major factors in accelerating this risk. Abnormalities of the triglyceride/high-density lipoprotein cholesterol (TG/HDL) axis are the most commonly observed lipid alterations in patients with T2DM and MetS. Often, there are associated reductions in the size and the cholesterol content of low density lipoprotein cholesterol (LDL-C). The small dense LDL-C even after treatment with statins result in an underestimation of the actual number of LDL particles in the blood because the LDL-C levels may not be elevated and not truly reflective of the underlying pathology. High TG, low HDL-C and small dense LDL-C, and increased numbers of LDL particles (hidden), which enter the vascular wall and are atherogenic, are referred to as the **lipid triad** and warrant aggressive treatment. Remember, LDL-C is only a surrogate marker for apoB, a better predictor of baseline and on-treatment risk *(Heartbeat* 99-May 05).

Signs of high risk (accumulation in the plasma of small dense, atherogenic LDL particles—a better indicator of ApoB) in a lipid profile with TG/ HDL axis disorders are:

- TG/HDL-C ratio > 3.5 (predicts small LDL size and/or lack of large HDL particles).
- TC/HDL-C ratio > 4 (predicts increased numbers of LDL particles).
- Elevated non-HDL-C (30mg/dL higher than LDL-C goal)—predicts increased numbers of LDL particles.

The identification of this scenario is an indication to work more intensively to reduce the known culprits, such as obesity and diabetes, which are growing to epidemic proportions and have become a major public health concern in the U.S. Otherwise, we run the risk of erasing the great advances that have contributed to the reduction in cardiovascular disease during the past 40 years.

What's really happening?

Moderately elevated TG in the presence of low HDL-C predisposes patients to increased vascular risk. VLDL and chylomicrons are the lipoproteins that transport TG. If a patient has increased TG levels, those lipoproteins will be increased in number and contain more TG. The TG-rich VLDL (large) and chylomicrons then transfer the TG using cholesterol

ester transfer protein (CETP) to the TG-poor lipoproteins in exchange for cholesterol. Thus VLDL sends TG to LDL and HDL in exchange for their cholesterol. The LDL and HDL become cholesterol poor and TG-rich. Enrichment of these particles with TG increases their susceptibility to lipolysis (hydrolysis or removal of TG) by hepatic lipase which, in the process, converts them to smaller, denser, more atherogenic LDL and smaller HDL which is vulnerable to renal excretion thereby reducing HDL-C.

When the TG (and lipoprotein surface phospholipids) are removed from such ApoB containing cholesterol poor particles, the particle itself collapses and becomes smaller, as it is now transporting only the reduced amount of cholesterol (the TG are now gone). Thus, even subtle increases in TG will shift HDL and LDL size from large to small.

The previously large VLDL (TG rich) lipoproteins now become TG poor and cholesterol rich small atherogenic apoB VLDL remnants represented by increased VLDL-C levels (TG/5; normal < 30 mg/dL).

NMR LipoProfile testing, which measures LDL size, and particle number (LDL-P), considered by most experts to be the gold standard to determine true CHD risk would show elevated LDL-P, pattern B small LDL and small HDL or reduced large HDL and elevated large VLDL. CV risk is most directly related to the number of particles. Entry of the apoB-containing LDL particles into the vascular wall is concentration driven.

No Surprises—Lifestyle a major factor

Life style changes in diet and activity levels are the prime therapy for T2DM and MetS with abnormalities of the TG/HDL axis. Reducing calorie intake, including reducing saturated fats and avoiding simple carbohydrates (and replacing them with complex carbohydrates in moderation) can decrease LDL-C and increase HDL-C. Increasing exercise (30 minutes 5x/week minimum, preferably daily) doesn't lower LDL-C, but it can improve insulin resistance and can decrease TG and increase HDL-C. Therapeutic lifestyle changes (TLC) are the first interventions that should be attempted in these high risk patients. However, achieving and maintaining sufficient TLC to limit CV risk is difficult. Therefore the combination of TLC and drug therapy is the optimal approach to risk reduction in patients with T2DM and MetS.

Pharmacotherapy:

When you see patients with TG/HDL axis disorders, you assume they have increased numbers of atherogenic apoB (small dense LDL particles or markedly increased LDL-P on the NMR report) and lack of large HDL. **The only proven treatment to reduce clinical events is to reduce the increased numbers of atherogenic apoB (LDL) particles.** That's why the NCEP Guideline recommendations list LDL-C as the primary treatment goal and non-HDL-C as the secondary treatment goal when TG is greater than 200mg/dL.[1] These are the surrogate markers for ApoB. Non-HDL-C is a better marker for ApoB especially when TG is high. The most efficacious way of reducing LDL-C is to prescribe a statin or statin/ezetimibe combo to get to specified goals.

Statins are the most widely used medications to reduce LDL-C and LDL-P levels and are known to significantly reduce CV risk. Statins work by up regulating LDL receptors (LDLr), clearing out atherogenic LDL particles which would otherwise enter the vascular wall. In the recent Collaborative Atorvastatin Diabetes Study (CARDS), a primary prevention study conducted in patients with T2DM, atorvastatin monotherapy was associated with a 37% reduction in the rate of major CV events, a 40% reduction in LDL-C, a 19% reduction in TG and a 1% increase in HDL-C.[2] This study provides further evidence that statins provide benefit and should be first line therapy in T2DM patients. NCEP III ½ (2004 Update) recommends a goal LDL-C < 70mg/dL in T2DM.[3] The American Diabetic Association recommends that all T2DM patients > 40 years of age be on a statin regardless of LDL-C level.[4] Head to head trials have shown that rosuvastatin (Crestor) is the most effective statin to lower LDL-C (up-regulating LDLr the most) and increase HDL-C. The problem is that significant residual risk can remain, especially in those with persistently high TG and low HDL-C.

Ezetimibe, another agent that reduces LDL-C and LDL-P, inhibits cholesterol absorption from the intestine, which reduces the amount of cholesterol in the liver and increases hepatic LDL receptor (LDLr) expression, resulting in greater uptake of particles

from the circulation. Thus it seems that statin and ezetimibe complement each other nicely to get LDL-C and non-HDL-C to goal. Unfortunately this may not be enough, especially when TG remains high and/or HDL-C remains low. Additionally, since there are no outcomes data with ezetimibe it should not be used as monotherapy.

Fibrates are a class of drugs that significantly lower TG and elevate HDL-C. The overall effect of fibrates is to decrease TG-rich lipoproteins, and to return both LDL particles to normal composition and HDL to normal remodeling. This means that with fibrate treatment, LDL particles become larger and more buoyant. Even though the total cholesterol may remain the same, the number of LDL particles tends to decline, and this is very important to decrease CV risk. In addition the larger LDL size makes these particles more susceptible to LDLr removal before entering the vascular wall. Fibrates by up-regulating hepatic SR-B1 receptors delipidate HDL creating small HDL. The cholesterol is then excreted in the bile and then the small HDL is available for relipidation.

Based principally on evidence from the Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT), data suggests that patients who have T2DM or MetS achieve substantial CV benefit with fibrate therapy. In VA-HIT, treatment was associated with greater than 30% reduction in CV events.[5] Interestingly, when compared to statin trials, gemfibrozil had greater absolute risk reduction and a lower number needed-to-treat in VA-HIT, raising the question of whether it should be moved to first-line treatment. At a minimum, the actions of fibrates along with their proven outcomes benefits make them a perfect addition to statins as combination therapy for patients with T2DM and/or MetS. For safety reasons we're obviously talking fenofibrates when we give fibrates in conjunction with statins.

Niacin decreases TG and increases HDL-C. It also increases the size of LDL particles. However because of its potentially negative effects on insulin resistance and poor tolerability it may not be the optimal lipid modifying agent to use in T2DM or MetS.

Omega-3 fatty acids (FA) have been shown to have beneficial effect both on TG as well as risk for cardiovascular events. They also increase HDL and increase size of LDL particles. Omega-3 FA have been shown to significantly reduce the risk for sudden death caused by cardiac arrhythmias and all-cause mortality in patients with heart disease.[6] They are also anti-thrombotic and anti-inflammatory. Fatty fish such as salmon and tuna, flaxseed, canola oil and walnuts are good dietary sources of omeg-3 FA. Two servings of fish per week or 1 gm of Omega-3 FA (Omacor) are recommended for prevention by the American Heart Association. Higher doses (2 to 4 g per day) are required to reduce elevated TG. Omega-3 FA can also be used to complement statins and/or fenofibrates to get lipids to goal.

Combination Therapy

Although lipid-modifying drugs are often used alone, regimens containing more than one drug may be more effective than monotherapies at reducing CHD risk because of complementary mechanisms of action on lipoprotein metabolism. In some cases the combination (additive effects) may enable one to reach appropriate goals of therapy where just one drug alone would not (statin/ezetimibe). In others, combination therapy would allow safer lower doses of a drug (statin) to be used while still attaining goal (statin/ezetimibe). This combination is particularly well suited for patients with significantly elevated LDL-C levels.

As mentioned previously, many patients with T2DM or MetS have elevated TG (> 150mg/dL) and low levels of HDL-C (< 40mg/dL). In such patients, an assessment of LDL-C may not accurately reflect risk from the increased number of LDL particles because of the reduced cholesterol content per particle. The complementary effects of a fibrate/statin combination has been shown to be significantly more effective than either drug alone in decreasing LDL-C and TG and increasing HDL-C levels. The better LDL-C reduction is in part related to the significant decrease in the proportion of small dense LDL particles and an increase in larger LDL particles with the statin/fenofibrate combination. In addition, both classes of medication have beneficial pleiotropic effects, including decreased inflammation and significant decreases in cardio-CRP levels along with proven outcomes benefits. The FIELD study results due to be presented at the American Heart Association meeting next month should give us more information about outcomes in 10,000 diabetics.

Conclusions/Recommendations

Abnormalities of the TG/HDL-C axis (mixed dyslipidemia) are part and parcel of insulin resistance seen in T2DM and/or MetS and contribute to the increased CV risk seen in these patient populations. The high TG and low HDL-C are the most commonly observed lipid abnormalities. Associated reduction in size and cholesterol content of LDL often leads to an underestimation of the number of LDL particles in blood. This is referred to as the lipid triad.

In reviewing the lipid profile, an elevated TG/HDL-C ratio (> 3.5) suggests that the predominant LDL particle size is small and that there is a lack of large HDL particles. LDL-C is not the only risk factor for heart disease. Increased non-HDL-C (usually > 100mg/dL) and/or TC/HDL-C ratio (> 4) predicts increased numbers of atherogenic apoB (LDL) particles—high LDL-P (concentration) per NMR LipoProfile. High numbers or concentration is directly related to high-risk. The TC/HDL-C ratio predicts small HDL size only if LDL-C is normal.

The first priority of treatment is to decrease the number of particles. Typically, the best way to do that is with statins, by up-regulating LDLr to remove the increased numbers of LDL particles and decrease risk (proven outcomes benefit). Ezetimibe can be used in combination with a statin as needed to get to appropriate LDL-C goals (usually < 70mg/dL) as described previously. It must be emphasized to patients that statins are not a credit card to eat indiscriminately and that TLC is an important component of therapy.

However, residual risk may still be present. If TG is still high, look at non-HDL-C and the ratios again. Assuming they are high, the patient still has too many small LDL (ApoB) particles. Combination therapy with fibrates (fenofibrates-Antara 130mg, Tricor 145mg or Triglide 160mg) will increase LDL size, making them more recognizable to the LDLr, and thereby enhance LDL particle removal by the statin or statin/ezetimibe up-regulated LDLr. Fenofibrates will also increase HDL particle size.

Omega-3 FA is beneficial and safe in combination with any of the above mentioned treatments.

There is ample evidence to believe that continued education of our patients about the benefits of TLC in combination with multiple drug therapy is well suited to treating the mixed dyslipidemia (lipid triad) of T2DM and MetS.

African-American Paradox

Fewer African Americans meet the criteria for MetS than do Caucasians, even though more African Americans have insulin resistance. This is apparently because TG and TG/HDL-C ratios are not reliable markers in African Americans.[7] This is due to the fact that these people have lipoprotein lipase polymorphisms that more effectively hydrolyzes TG.

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