LIPID CASE 270 Do TG require therapy?

I get a lot of e-mails related to a multitude of lipid/lipoprotein issues and I wanted to share the following one with you. The correspondence came from a PhRMA representative who was having a frustrating experience discussing triglycerides (TG). Of course their correct biochemistry term is triacylglycerols.

The rep stated: I was hoping you could provide some guidance in regards to a conversation I had with one of my cardiologists the other day: We were discussing how after LDL-C is at goal, the need-to-treat non-HDL-C when TGs are over 200 and how TG-modulating drugs (the rep named his particular product) are an option to use to lower TGs which in turn will lower non-HDL-C. The cardiologist objected, essentially saying *"I feel that TGs are all lifestyle/diet driven and so I can't justify drug therapy. I see elevated TGs and I think too many carbs and simple sugars. LDL and HDL are more genetically determined and justify drug therapy but not TGs."* Other than re-enforcing the need to get to the secondary non-HDL goal and discussing how TGs are a major "driver" of non-HDL-C, how would you recommend I respond to this objection?

DAYSPRING DISCUSSION:

Easy: Anyone who has read and comprehended the NCEP ATP-III Guidelines knows that in patients at LDL-C goal (on a statin and lifestyle) if the TG are still elevated or the TG are still high and HDL-C is low, NCEP stated that additional therapy is needed: that therapy suggested in 2001 was higher statin dose, more aggressive lifestyle, or in high risk patients adding a fibrate or niacin. Since then ezetimibe (Zetia) plus statin has received a non-HDL-C indication from the FDA and Lovaza (prescription strength omega-3 has no such indication but there is data in its package insert it with statin improves non-HDL-C). So if the doc had a patient on lifestyle and appropriate statin therapy (to get to LDL-C goal) he would be dismissing the NCEP guidelines that certainly justify drugs to achieve non-HDL-C goal. For Lipidaholics who like a more involved discussion, read on.

Unfortunately the above response to the rep was spoken by a cardiologist, who is likely a very skilled interventionist but has very little up to date (post 2001), serious lipid/lipoprotein knowledge. His statements should make us all laugh or cry (for the patient). The doc is certainly not a subscriber to Lipidaholics Anonymous. Even more unfortunate is that cardiologists for the most part typically see high or very high risk patients and thus are entrusted with keeping the sickest of the sick alive, meaning out of the CCU, out of the cath/stent lab, out of the bypass OR and ultimately keeping ASHD off of the death certificate. Cards (any anyone else seeing high risk folks) must understand the risk associated with triglycerides and simply cannot be timid in their treatment recommendations in such patients. They are obligated to stay on top of the literature and must follow guidelines and indeed if we are to really make go beyond guidelines on a case by case basis.

Twenty years ago the noted William Castelli in his classic "Epidemiology of triglycerides: a view from Framingham" [Am J Cardiol. 1992;70(19):3H–9H] and much more recently N. Sarwar et al. in "Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies [Circulation. 2007;115(4): 450–458] stated TGs are a significant risk factor for CHD irrespective of LDL-C levels and other established risk factors. I suspect the card believes that, but clearly he sees no need for treatment beyond lifestyle. Amazingly he cannot see a justification for TG-modulating pharmacotherapy.

I wish providers of a similar mind set would closely examine the trials of their beloved statins (note: unless not tolerated virtually all of my patients are on statins) and see that the vast majority of CV events continue to occur in statin-treated patients. This is called residual risk and several studies including the PROVE-IT trial (high dose statin trial using atorvastatin (Lipitor) 80 mg and pravastatin 40 mg) showed even when LDL-C is < 70 mg/dL, the highest residual risk is in those with elevated TG levels. Indeed in those who had an LDL-C < 70 mg/dL and a TG < 150 mg/dL there was an additional 26% event reduction compared to those at LDL-C goal but with TG > 150 mg/dL. The authors concluded: *"On-treatment TG <150 mg/dl was independently associated with a lower risk of recurrent CHD events, lending support to the concept that achieving low TG may be an additional consideration beyond low LDL-C in patients after ACS"* (J Am Coll Cardiol 2008;51:724–30).

The first silly statement made above is that TG unlike cholesterol (LDL and HDL) is lifestyle not genetically driven. The truth is that all lipid disorders need lifestyle to be part of the therapy [in an ideal world (certainly that does not include NJ) all patients would do that to the max]. Why do we need so many nutritionists, if in the mind of the card cholesterol (LDL and HDL) treatment, unlike high TG, justifies drug therapy? His belief is nutritionists are great at TG-lowering but cannot help modulate LDL-C and HDL-C? In fact, **all** lipid abnormalities including cholesterol, fatty acids and TG are driven first by genes and second by lifestyle. Does the provider not encourage lifestyle in is patients with cholesterol abnormalities? Does he know the high carbs he fears are the major stimulus for cholesterol production. He should go check where the body gets excess acetate as he might find it is related carbs intake and catabolism. In the 37 step cholesterol synthesis pathway, the first step is the conversion of acetate or acetoacetate (a carbohydrate or FA derivative) to HMGCoA.

The cardiologist might also be shocked to learn that there are just as many genes and nuclear transcription factors regulating TG synthesis and catabolism as there are cholesterol. In fact a article from the Thematic Review Series Genetics of Human Lipid Diseases entitled Genetic determinants of plasma triglycerides by Christopher T. Johansen, Sekar Kathiresan, and Robert A. Hegele was just published (J. Lipid Res.2011;52:189–206). The authors have zeroed in on 15 such genes. They state: *"More complete understanding of the genes and variants that modulate plasma TG should enable development of markers for risk prediction, diagnosis, prognosis, and response to therapies and might help specify new directions for therapeutic interventions."* Of course

until such testing appears, we have to use other now available tests and strategies to reduced risk in patients with TG abnormalities (did someone say apoB?).

So as Ronald Reagan might say: THERE HE GOES AGAIN - Let me once again describe that there are two reasons why TG are in the United States today are driving atherogenesis and TG per se MUST be treated in patients with CV risk: but keep in mind there are no TG in the plaque - only sterols. You will see that TG have everything to do with the trafficking of sterols into the artery wall. Those who have heard me lecture often say I consider TG to be the driver of the getaway car! Sterols cause plaque but in many patients, especially those with insulin resistance (IR) sterols would have never entered the plaque if there were no TG abnormalities.

CONDITONS REQUIRING TG TREATMENT: usually with meds

SCENARIO ONE: Severe Hypertriglyceridemia: defined as fasting levels > 500 mg/dL. The risk here may or may not be atherosclerosis, but is surely acute pancreatitis. Severe TG levels >1000 mg/dL are associated with approximately 10% of all acute pancreatitis episodes and half of all cases of gestational pancreatitis. It has been suggested that high levels of circulating TG-rich lipoproteins are hydrolyzed by pancreatic lipase into FAs. The elevation in serum FAs may induce the formation of FA-phospholipid micelles that disrupt pancreatic membranes, and subsequent inflammation due to the disruption of platelets and the vascular endothelium. Hyperviscosity due to elevated serum FAs may also aggravate this condition (Curr Opin Lipidol. 2009; 20(6):497–504).

SCENARIO TWO: Much more common and applicable to the case under discussion. TG levels < 500 mg/dL (typically between 150 -500, but often even 70-150 mg/dL). These levels are usually associated with IR and high CV risk. Indeed, very recent analysis of NHANES data showed the majority of atherothrombotic events now occurring are related to IR cannot be explained by any LDL-C abnormality but rather by apoB and the most suggestive components of the lipid profile in patients with cardiometabolic risk are elevated TG, low HDL-C (the so called TG/HDL axis disorder: please read Szapary PO, & Rader DJ. The triglyceride– high-density lipoprotein axis: An important target of therapy? Am Heart J 2004;148:211–21), high VLDL-C (remember VLDL-C = TG divided by 5), abnormal TG/HDL-C (> 3.0) and/or elevated non-HDL-C in the face of normal LDL-C [the non-HDL-C being driven not by LDL-C but rather high VLDL-C (TG) or low HDL-C or both].

IR patients, for genetic and lifestyle reasons have too much FA and glycerol (the substrates from which TG are synthesized). Their hepatic pools of fat (TG) increase and the liver goes into action to send the TG (3 fatty acids) to muscles for oxidation and energy creation or to adipocytes for energy storage. To accomplish this, the liver must produce TG transportation vehicles, called very low density lipoproteins (VLDL): these large particles enwrapped with a single molecule of apolipoprotein B (apoB) carry a minimum of 5 times more TG than cholesterol and cholesteryl ester (hence VLDL-C = TG/5). In the livers of those with elevated TG there will be increased production of large

VLDL-P and thus apoB rises (ATVB 2005;25:1697-703 and Diabetalogia 2006;49:755-65).

Next the card should read: Overproduction of very low–density lipoproteins is the hallmark of the dyslipidemia in the Metabolic Syndrome by Martin Adiels et al. The authors state: *"Recent evidence suggests that a fundamental defect is an overproduction of large very low–density lipoprotein (VLDL) particles, which initiates a sequence of lipoprotein changes, resulting in higher levels of remnant particles, smaller LDL, and lower levels of high-density lipoprotein (HDL) cholesterol. These atherogenic lipid abnormalities precede the diagnosis of type 2 diabetes by several years, and it is thus important to elucidate the mechanisms involved in the overproduction of large VLDL particles."* **THERE YOU HAVE IT. Elevated TG should be an immediate warning sign to the treating physician that no matter what the LDL-C is, apoB, the single biggest risk factor for atherogenesis and adverse clinical events is almost always elevated and the apoB-containing atherogenic particles that carry sterols into the artery wall are cholesterol-rich VLDL and chylomicron remnants, IDLs, large TG-rich, cholesterol-poor LDLs or small, cholesterol poor LDLs (note > 90% of those particles will be cholesterol-poor LDLs).** None of these incredibly atherogenic particles can under any circumstances EVER be diagnosed by looking at LDL-C. These particles are the major reason NCEP ATP-III added non-HDL-C (the poor man's apoB) to the guidelines. Worsening the scenario is the very low total HDL-P in these folks. Of course, the problem with non-HDL-C (although it is a superior apoB surrogate than is LDL-C) is that apoB and LDL-P can still be high in a large number of patients with at goal non-HDL-C. Thus high TG is usually a powerful signal that apoB and LDL-P must be reduced to goal and that usually requires meds

So for a more thorough review: Physiologically normal sized VLDLs [protein enwrapped TG and phospholipid (PL) transportation vehicles] undergo rapid lipolysis [lipoprotein lipase (LPL) induced hydrolysis of core TG in muscle and adipocyte vascular beds]. Surface apoC-II on VLDLs bind to and activate LPL which after loss of core TG and surface PL become IDLs and are rapidly cleared by hepatic LDL receptors (note as the VLDL releases in size, large amounts of surface PL are released and picked up by phospholipid transfer proteins): some of the IDLs undergo further lipolysis (of core TG and surface PL) by hepatic lipase and become LDLs which are then cleared over 1.5 to 3 days by hepatic LDL receptors (LDLr). If one is producing normal numbers of properly sized VLDLs, they and their progeny (IDLs and LDLs) are cleared and there will be no excess of apoB particles to enter the arterial wall. Normal VLDL half life is 2 to 6 hours and for IDLs 1-2 hours. A chylomicron is one hour. For completeness and for especially lipidologists reading this paragraph, also crucial to VLDL and chylomicron lipolysis are apoA-V and an endothelial cell protein, glycosylphosphatidylinositol (GPI)-anchored high-density lipoprotein-binding protein 1 (GPIHBP1). Boy that is some mouthful isn't it? If you are not familiar with GP1HBP1 please see Beigneux et al Current Opinion in Lipidology 2009, 20:211–216.

No what happens in the IR patient with abnormal lipoprotein physiology? As mentioned there will be production of too many large VLDLs. Once released, large TG-rich VLDL-

P (a proven marker of insulin resistance and used by LipoScience to calculate lipoprotein related insulin resistance score) tends to have increased plasma residence time for several reasons: 1) because of the increased number TG-enriched large VLDLs there is increased competition between themselves and chylomicrons for lipoprotein lipase (the expression and activity of which is typically reduced in IR and T2DM patients). 2) Further delaying lipolysis in IR patients is the IR induced increase in hepatic production of apo C-III which once attached to TG-rich lipoproteins like VLDLs delay their lipolysis (apoC-III interferes with the necessary binding of apoC-II to LPL, displaces or blocks VLDL apoE needed to attach to VLDL receptors in muscles and adipocytes) The plasma residence time of these TG-rich monster particles is increased to 12-16 hours: leading to both postprandial and fasting hypertriglyceridemia. This increases plasma viscosity, down regulates endothelial nitric oxide, induces expression of inflammatory factors, increases coagulation factors (PAI-1 and fibrinogen), etc.

The increased plasma residence time of these TG-rich lipoproteins increases the activity of an HDL trafficked (carried) lipid transfer protein called apolipoprotein D or better known as cholesteryl ester transfer protein (CETP). This protein swaps neutral (non-acidic) lipids between any and all lipoproteins. This means lipoproteins can exchange their core lipids, one molecule of cholesteryl ester (CE) for one molecule of CE or one molecule of CE for one molecule of TG. Exchange (heterotypic) can occur between HDLs (apoA-I particles) and apoB particles (chylos, VLDLs, IDLs and LDLs), or the exchange (homotypic) can be between various HDL subspecies or between the various apoB particles (i.e. VLDLs can exchange lipids with LDLs). Heterotypic exchange will change the core lipid composition of the involved particles: i.e. HDLs and LDLs become CE-poor and TG-rich and VLDLs and chylomicrons become TG-poorer and CE-rich. TG-rich LDLs and HDLs when exposed to hepatic lipase become smaller and denser. Very small HDL is prone to dissolution and rapid renal excretion of its apoA-I, leading to low HDL-C, reduced large HDL-P, reduced large HDL-C and reduced total HDL-P. Small LDL is not as rapidly recognized and cleared by LDL receptors, leading to the very high LDL-P and apoB so typical in these patients with TG abnormalities.

The other faulty aspect of the statement made by the provider above is that he is oblivious to the fact that a major determinant of low HDL-C in IR patients is elevated TG: IR patients with TG > 70 mg/dL may have increased CETP activity which transfers cholesterol in exchange for TG between HDLs and apoB particles like VLDL and LDL. As discussed, because the patients HDLs are now carrying TG instead of cholesterol, HDL-C is almost always low. The patients have high apoB (LDL-P) and low apoA-I (HDL-P). The best way to begin to raise HDL-C is to reduce TG and CETP activity: something a fibrates, niacin and omega-3 FA (in persons with very high TG) do quite well.

If you follow the above two paragraphs you will see until proven otherwise patients with TG elevations likely have very high apoB (LDL-P)(and very low apoA-I (HDL-P). Amazingly at a TG of 130 mg/dL 1/3 of patients have elevated LDL-P, at a TG of 150 mg/dL 50% and at a TG of 200 mg/dL over 80%. They also have very high TC/HDL-C ratios, apoB/apoA-I ratios and LDL-P/total HDL-P ratios. In the VA-HIT trial (a trial of

high risk men with low HDL-C, elevated TG and unremarkable LDL-C) the best predictor of baseline risk was the LDL-P/HDL-P ratio (Circulation. 2006;113:1556-1563). We know from the INTERHEART studies (Lancet 2008; 372: 224–33) and AMORIS (Lancet 2001; 358: 2026–33) how very powerful the apoB/apoA-I ratio is. And of course looking at ancient lipid history we know from Framingham, that TC/HDL-C was a great predictor of risk (indeed in Framingham risk scoring only the only lipids considered are TC and HDL-C in its risk equation). So if the cardiologist under discussion would start looking way beyond LDL-C and checked out the TC/HDL-C ratio, non-HDL-C, or better yet apoB/apoA-I ratio or best of all LDL-P/HDL-P ratio he would not make silly statements that TG do not require pharmacologic therapy! In addition he is delusional if he thinks all patients do the very serious lifestyle changes necessary to lower LDL-P and apoB to goal (see Diabetes Care 2008;31:811-822, Clinical Chemistry 2009;55:3:407–419 for organizations providing apoB and LDL-P goals)

So if an insulin resistant patient of the cardiologist with high TG was on lifestyle plus a statin or statin/Zetia and the TG were still high - he would not offer a fibrate (or other TG-synthesis inhibitor like niacin or high dose omega-3 fatty acids): I would then say he is ignoring the just cited guidelines that we currently have and would certainly be under treating. If in fact the TG are still high, then VLDL-C has to be high and it would be very likely HDL-C is still low. Despite the normal LDL-C, non-HDL-C would not be at goal. Ignoring NCEP goals is surely substandard care and borders on malpractice. Again why does anyone think NCEP inserted Non-HDL-C as a secondary goal if the only important thing is LDL-C? Note to all: for as good as statin monotherapy (even high dose) are in reducing LDL-C they are less efficacious at normalizing non-HDL-C (Am J Cardiol 2005;95:360–366) and somewhat pathetic at normalizing apoB or LDL-P (Journal of Clinical Lipidology 2008;2:36–42).

My approach to reducing TG-related apoB and LDL-P in my patients (and since I use Health Diagnostic Labs (HDL) Advanced Profile (see www.myhdlcom) on all patients and therefore get NMR parameters and apoB on everyone) is lifestyle for all (and thanks to Health Coaches provided as part of their service by HDL my patients receive nutritional advice - some follow and some do not). I am aggressive with apoB reducing therapies: that means LDL receptor (LDLr) upregulating therapies as first line drugs: statins are the best - but most of their LDLr upregulating potency is with the lower starting doses (rule of 6 after that with each titration): additional LDLr upregulation can be achieved with ezetimibe (Zetia) or colesevelam (Welchol) or plant stanols (Benecol). If still not at apoB/LDL-P, non-HDL-C goal then TG-synthesis inhibitors (my word) must be used: this includes fibrates or fibric acids, niacin (preferably extended-release) or high dose omega-3 (N3) fatty acids. The TG synthesis inhibitors reduce VLDL production (lowering apoB), reduce VLDL core TG and enhance catabolism of TG-rich lipoproteins (reduce apoC-III, increase LPL activity, decrease CETP activity) further reducing apoB and all of the above described pathologies associated with high TG.

Although it would take a large review, how does one choose between the three TG-synthesis inhibitors mentioned above. 1) Diabetics with TG > 200 mg/dL get substantial microvascular benefits (off label use) from fenofibrate (DAIS, FIELD, ACCORD) and

thus must be considered in T2DM. 2) Niacin if used at 2000 mg daily has a lot of powerful positive vascular imaging data. 3) In persons with high TG, I always consider Omega-3 FA in patients with a low Omega 3 Index (a test I now get on all my patients (see www.onmegaquant.com). We all know that Omega-3's at 4 grams can help us in our TG battles, but I also believe a major benefit in normalizing the Omega-3 index is that our phospholipids will be enriched with EPA and DHA and all of our cell membranes will be far healthier and better prepared to do proper cell signaling conceivably leading to numerous health benefits. Note: Lovaza (my preferred choice of omega-3 products) is only FDA approved to treat very high TG levels but close reading of the package insert revealing data from COMBO trial shows it is helpful with TG < 500 mg/dL when combined with statins.

Finally the rep asked: Other than re-enforcing the need to get to the secondary non-HDL goal and discussing how TGs are a major "driver" of non-HDL-C (I paid attention to your lectures), how would you recommend I respond to this objection?

Simply, I would try and educate him that achieving non-HDL-C goal is guideline mandated and is simply a poor man's surrogate of elevated apoB or LDL-P which are the single biggest risk factors for atherogenesis. By not treating TG and normalizing (VLDL-C) and hence non-HDL-C, you are extremely likely allowing increased levels of apoB (LDL-P) to persist drastically creating residual risk. Those apoB particles present when TG are high are small LDL, large TG-rich, CE poor LDL and remnants (VLDL and chylomicron): all killer particles none of whom have any relationship to LDL-C but all of whom are related to TG. It is very likely that non-HDL-C will assume greater significance in ATP IV coming later this year.

CASE CLOSED