

In the Paris Prospective Study looking at diabetic men as well as those with impaired fasting glucose over an 11 year period, CV death was statistically significantly associated with a TG > 133 mg/dL (Diabetologia 1989;32:300-304). In data from Framingham, 2/3 of women who had a CV event had an LDL-C < 140, but all had either a high TG (>200 mg/dL) or a high TG with a reduced HDL-C (Arch Intern Med. 2001;161:949-954). In obese women (waist size > 35 inches), CV risk is associated with TG > 128 mg/dL (Circulation 2005;111:1883-1890). If you would like to see dozens of other studies linking CV morbidity to TG at very low levels (low 100s) visit www.lipidcenter.com and click on Professionals and scroll down to the PP slide deck on Atherothrombosis and TG.

NCEP ATP-III in 2001 stated a TG of 200 mg/dL is associated with high CV risk and a TG of > 500 mg/dL with very high risk. NCEP went on to say that if a person was not overweight, exercised, did not have an endocrine problem, was not using certain drugs, did not smoke the TG should never be above 100 mg/dL. If some of those were present the levels would rise to 150-199 (with the most common reason being obesity and lack of exercise). For those with genetic problems, the TG can rise to > 200 mg/dL. Is everyone listening: A TG > 100 mg/dL is potentially ABNORMAL. Noninsulin resistant populations have fasting TG of 10-70 with a mean of 30 mg/dL. Normal postprandial excursions are 30-100 mg/dL: thus anyone with a PP TG of > 170 has a pathological TG condition (The TG Tolerance test: Diabetes Care 27:89-94, 2004). If you see a TG of 200 mg/dL do not waste your time asking if the patient was fasting or not: that level is abnormal in either case. Never bring the patient back fasting to repeat the TG. It might drop to below 150 and you would erroneously believe that is normal.

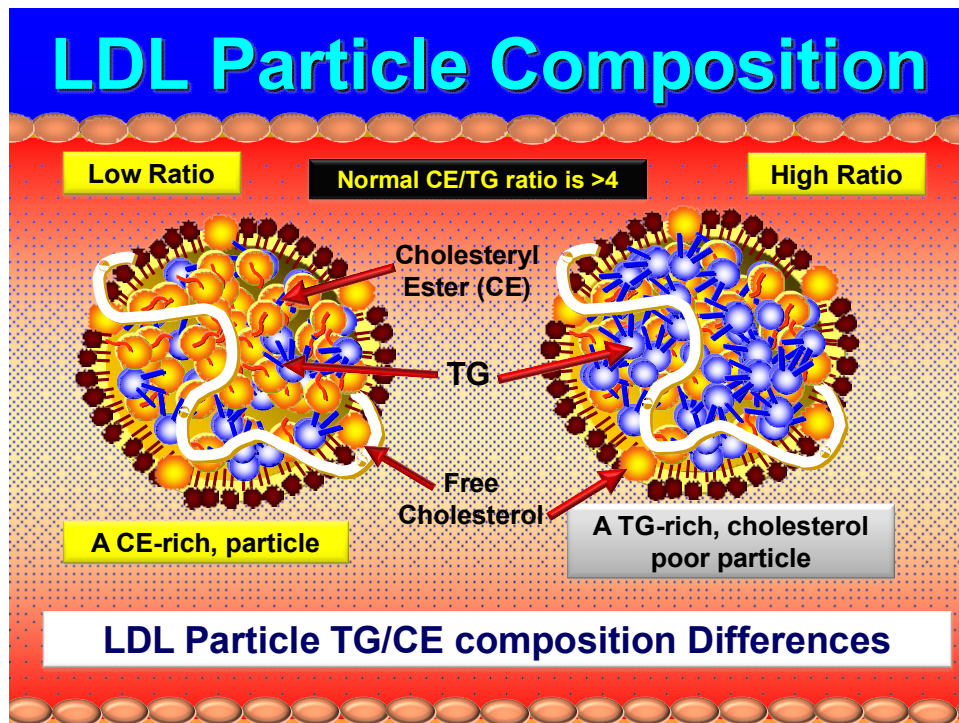
A key concept related to TG is the Friedewald formula where VLDL-C = TG/5. Thus with a TG of 150, the VLDL-C is 30. The formula makes certain assumptions. All TG are in VLDLs and VLDL composition is 5/1, i.e. a VLDL has five times more TG in its core than cholesteryl ester. With physiologic levels of TG (10-70), the vast majority of the TG are in VLDLs. However as TG levels rise, other lipoproteins, specifically IDLs, LDLs and HDLs also become overloaded with TG and the VLDL composition changes from the 5:1 ratio. That is why the Friedewald formula cannot be used to calculate either VLDL-C or LDL-C as TG rise. Many labs state the formula is accurate with TG up to 400, but few lipidologists agree with that. Note that LDL-C = TC - [VLDL-C + HDL-C].

The following is obvious and explains so much of what you all see every day. Above I stated that as TG levels raise IDLs, LDLs and HDLs become TG-rich. How does that happen? If the liver overproduces and secretes increased numbers of TG-rich VLDLs (or the jejunum does the same with chylomicrons) serum TG levels will obviously increase. If these particles do not undergo rapid lipolysis (fat breakdown) they will have increased half life's or plasma residence times and postprandial hypertriglyceridemia occurs. Lipolysis is the hydrolysis of lipids like TG (triacylglycerol), cholesteryl ester, or phospholipids. Hydrolysis is the chemical reaction where water (or H or OH groups) is formed by separating molecules: the hydrolysis of triacylglycerol or TG results in the release of one or two fatty acids (acyl groups) resulting in diacylglycerol, monoacylglycerol and FA. A TG-rich lipoprotein with increased plasma residence time can create a lot of havoc.

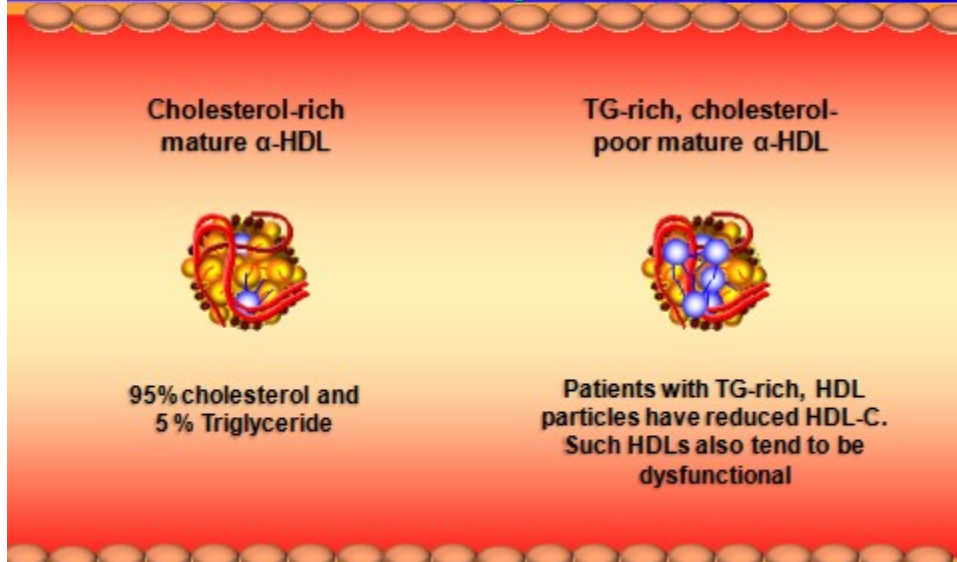
- They increase blood viscosity
- They create endothelial dysfunction by down regulating NO production
- They are associated with abnormal coagulation markers (PAI-1, fibrinogen)
- They are associated with elevated apoC-III an independent risk factor for CHD (see ref 2 below)
- They are associated with insulin resistance
- They traffic Lp-PLA2
- They are associated with increased numbers of atherogenic remnants
- They are associated with increased cholesteryl ester transfer protein (CETP) activity
- Since FA can become soaps (detergents), they destroy cell membranes (especially in pancreatic cells)

The increased CETP activity is crucial to TG's ability to create lipoprotein havoc. This protein swaps one molecule of TG for one molecule of cholesteryl ester (CE) between lipoproteins. The VLDLs and chylos (TG-rich particles) send their TG to LDLs and HDLs -- to make room for the arriving TG, the HDLs and LDLs send CE back to the VLDL or chylo. In effect, the LDLs and HDLs become TG-rich and CE-depleted whereas the VLDL (and chylo) becomes CE-rich. The particle sizes remain the same: the only thing that has happened is a transfer of core neutral lipids. If you take a moment to think of these compositional changes in terms of the lipid profile the following axiom develops:

As TG VLDL-C and CETP levels rise there will be a fall in VLDL (and chylo) TG content and a rise in LDL-TG and HDL-TG. Well, an LDL and HDL carrying TG is a pathological lipoprotein. Their physiologic function is to traffic CE, not TG. If you have a lot of LDLs and HDLs carrying TG they contribute to the endothelial dysfunction, coagulation and blood viscosity conditions described above. TG-rich HDLs are usually quite dysfunctional and are less likely to perform cardioprotective actions - i.e. TG-rich, CE poor HDLs are dysfunctional.



High Density Lipoprotein Core Composition



Let's take this one step further:

If LDL-C and HDL-C goes down, and VLDL-C goes up -- what happens to non-HDL-C? The obvious answer is it goes up and remember non-HDL-C is simply a surrogate of apoB or LDL-P (atherogenic particles if present in increased numbers). Non-HDL-C is the secondary goal of therapy on NCEP. You have just learned what you probably already knew but never verbalized. Elevations of TG in the vast majority of cases is a surrogate increased apoB (too many LDLs and remnants). Also when using non-HDL-C remember it is influenced by VLDL-C (TG/5). Anyone with a high TG, has a high VLDL-C. If LDL-C is fine and VLDL-C is high, non-HDL-C will also be high. This is an easy way to spot someone at risk despite an at goal LDL-C.

Thus do not be fooled by dropping LDL-C levels as TG rise: the LDLs are simply carrying TG instead of CE. Do not be dumb enough to tell a patient with high TG but normal LDL-C (like menopausal women or metabolic syndrome patients) that they are fine and are at goal. If you would simply stop being one of the 80-90% of providers who do not calculate non-HDL-C you would see the risk. Anyone with a normal LDL-C but a high non-HDL-C is at risk as they still have too many apoB particles in their plasma. The CE that used to be in their LDLs and HDLs are now in the VLDLs (chylols) and you would know that if you took the time to calculate and use VLDL-C.

The process is not over with: If you are still with me you realize that CETP simply swaps TG for CE and the LDLs and HDLs are afterwards carrying TG instead of CE. This lipid swap did nothing to the size of the HDL, LDL or VLDL particles. However, as the VLDLs (chylols) enter vascular beds in myocytes and adipocytes they are exposed to lipoprotein lipase (LPL) and undergo further hydrolysis of the remaining TG. LPL does not hydrolyze CE. Thus the VLDLs lose their TG but not their CE. As they lose TG they shrink and chunks of the surface phospholipids break off and are picked up by phospholipid transfer protein for use elsewhere. The resultant (post lipolytic) VLDL (or chylo) is smaller and now carrying predominantly CE: these are termed remnant lipoproteins and numerous studies have shown they are associated with increased CV risk (through a variety of mechanisms). NCEP stated that anyone with a TG > 200 has increased remnants which convey CV risk CV risk not explained by their LDL-C levels. Thus VLDL-C is the poor man's remnant lipoprotein assay! Those doing NMRs can simply look at VLDL-P subparticle concentrations. What about the TG-rich, CE poor HDLs and LDLs. They are not substrates for LPL but as they pass through the liver they are substrates for hepatic lipase which is capable of hydrolyzing both TG and surface phospholipids. The LDLs and HDLs lose the TG but not their CE: they shrink and turn into small particles. Sometimes the HDLs are made very small or they release surface apoA-I which is vulnerable to renal excretion (ultimately causing low HDL-P or apoA-I and further contributing to the drop in HDL-C). The small LDLs are too large for renal excretion. However they are not readily recognized by hepatic LDL receptors and small LDLs have longer half life's than larger ones, explaining why most folks with small LDLs have such high LDL-P (apoB) levels. This was first described by apoB guru Alan Sniderman way back in olden times (in *Atherosclerosis* 1991;89:109-116). SO IT IS NOT REALLY THE SIZE OF THE LDL THAT CREATES HAVOC BUT RATHER IT IS THE PARTICLE CONCENTRATION, AND THE VAST MAJORITY OF FOLKS WITH SMALL LDL HAVE VERY HIGH LDL-P (APOB) LEVELS. There are other attributes of the small LDL that contribute to its atherogenicity, but particle # is the most critical.

I want to expound further: As mentioned, NCEP states, that high TG (and its association with remnants) convey CV risk way above that predicted by LDL-C. But the vast majority of folks with remnants also have tremendous elevations of LDL-P (apoB). So is the risk due to the VLDL remnants or LDL particles or both? I believe it is both as remnants aggravate disease through mechanisms other than entering the arterial wall. With respect to what particle is dumping cholesterol in the artery it is the LDLs. In Bill Cromwell's analysis of Framingham (a year ago in *J Clin Lipidol* 2007;1:583-592) he demonstrated:

" Not only was non-HDL-C more weakly related to incident CVD than LDL-P, the risk prediction given by LDL-P was improved only slightly by taking into account the contribution of VLDL-P. This latter finding is perhaps not surprising, given that VLDL-P constitute only a small fraction (about 5%) of the total number of atherogenic VLDL + LDL-P. Even when triglycerides are significantly elevated, VLDL-P numbers are only modestly higher because the excess triglyceride is carried predominantly by large VLDL-P, which are relatively few in number. Furthermore, in terms of the percentage of total atherogenic particles, VLDL-P levels are not very different in persons with high triglycerides because these same individuals also typically have elevated numbers of LDL-P that are smaller than average."

With a TG > 500 mg/dL, the first mission to eliminate the risk of pancreatitis. If HgbA1C is high - normalize that or get it below 7. A statin is an inappropriate first line therapy for TG > 500 mg/dL. We need to inhibit TG synthesis in a big way: reduced caloric diet, exercise, no alcohol of course: Then drugs that inhibit TG synthesis: First line therapy is 4000 mg of N-3 (previously called omega) fatty acids (Lovaza) plus fenofibrate (TriCor). Each can lower this level of TG by 50%, but with monotherapy it will still be too high so I use both. That should get the TG under 500 and then non-HDL-C becomes the goal of therapy. One must add a statin (high dose) or statin/ezetimibe combo. The two most efficacious statins on lowering TG are high dose Crestor or Lipitor.

However TG is not our goal; Non-HDL-C, apoB or LDL-P is the goal. Crestor is superior to Lipitor on Non-HDL and apoB parameters. Statin/ezetimibe would also be as powerful. How do drugs

like statins or ezetimibe lower TG? They upregulate hepatic LDL receptors which endocytose all apoB particles including VLDLs carrying TG. One note of caution: the patient had some abdominal pain: cholelithiasis has to be ruled out because the package insert warns against using a fibrate if gallstones are present. However in the FIELD trial they recruited several patients with gallstones and the fenofibrate did not aggravate their condition or cause new gallstones in the remaining patients. Thus if fenofibrate by increasing biliary cholesterol causes gallstones, the incidence is very, very small and in this patient the benefit would outweigh the risk. There is also a very tiny risk of pancreatitis with fibrate. Again in this case the benefit of a fibrate would outweigh any risk.

A word about using Lovaza: to lower TG, a threshold dose of 4000 mg is required. I find it so sad that some providers only, prescribe 1-3 grams of N-3 FA to lower TG. Also if one had ordered a direct LDL-C measurement in this woman, after Lovaza, TriCor or both are prescribed it is very likely LDL-C will go up. WHO CARES? As the TG fall the LDLs go back to carrying CE instead of TG - of course LDL-C rises. However at the same time there is a drastic fall in VLDL-C and a rise in HDL-C (as the HDLs go back to trafficking CE instead of TG). Even with LDL-C rising, Non-HDL-C drops, indicating a reduction in apoB particles. Any rise in LDL-C in the face of a dropping apoB is explained by particle composition changes. Despite the rising LDL-C, LDL-P drops. **Anyone** who stops Lovaza (N-3 FA) or TriCor (or fenofibrate) or the newly approved Trilipix (fenofibric acid) because of a rising LDL-C or an attenuation of the statin induced LDL-C reduction (despite a falling non-HDL-C) DEMONSTRATES THEY HAVE LITTLE LIPOPROTEIN KNOWLEDGE and they are brainwashed with the meaning LDL-C. If you want to see what a fibrate or N-3 FA is doing in a patient with high TG, follow VLDL-C and non-HDL-C: following LDL-C by itself is a useless waste of time. If you want to make life really easy, simply follow non-HDL-C (the NCEP goal of therapy).

