

LIPID CASE 249 End of the Lipid Era

Question (?) Surprise me with the correct answer: Who said and when did they say: *"In a desire to use more specific terminology, certain durable nouns from the **lipid era** should not be discarded."* The nouns being referred to are hypercholesterolemia and hypertriglyceridemia. Next question - if that is true, when did the lipid era end and what followed it? Third and final question: how many practicing physicians and lipidologists know the lipid era has ended? ANSWER IS BELOW!

New year's Wish: Wonder what will be new in lipoproteinology this year? NCEP ATP-IV should make its appearance. I would hope they will move to a lipoprotein based guideline similar to ADA/ACC and simply make apoB and LDL-P as the goals of therapy. The evidence supporting that over any type of cholesterol measurement continues to multiply. However, being a realist I suspect the most we can hope for is for non-HDL-C to replace LDL-C as the best marker of when to initiate therapy and as the goal of therapy. At least that will allow TG to finally receive its due (As TG rise, LDLs and HDLs become TG-rich and cholesteryl ester poor, as the VLDLs become CE-rich, explaining the typical dyslipidemia profile: high VLDL-C, normal to low LDL-C, low HDL-C and of course high non-HDL-C). Those in the know should realize that rising TG (starting > 100 mg/dL) with low HDL-C are simply a marker of too many atherogenic apoB particles, the vast majority of which are LDLs.

The real value of non-HDL-C is, not that it is some marker of VLDLs or remnants, but that it is simply the lipid measurement that best correlates with LDL-P. The real world problem is that as good as the correlation is, there is still significant discordance between it and LDL-P. Sometimes this can be predicted by high TG or especially high TG and low HDL-C, but in many patients it cannot be. Thus without particle quantification measurements, therapy becomes guesswork. Many are thus under treated and many are over treated. This is why it is also absurd for a clinician to simply state that "I just lower LDL-C well under 70 (or whatever) in every one." There are folks with significant elevations of LDL-C with no increase in atherogenic particles and of course there are patients with severe disease with LDL-C well below 70 mg/dL with still very high particle counts.

So my New Year's wish is that NCEP will do what the 2006 Ten-Country, 30 Member Panel International Position Statement, 2008 ADA/ACC Consensus Statement and 2009 AACC Statement did: mandate apoB or LDL-P as the preferred test for risk assessment and treatment goal.

To answer the question posed above: During the Christmas break I had the opportunity to sit down and carefully read one of the more important lipid manuscripts ever written. For those of you serious about lipids please obtain and read the following pentology published in 1967 (267:33-44, 94-103, 148-156, 215-225, and 273-281) in the *New England Journal of Medicine*: **FAT TRANSPORT IN LIPOPROTEINS - AN INTEGRATED APPROACH TO MECHANISMS AND DISORDERS**. The following three LIPID GODFATHERS authored this thorough treatise

DONALD S. FREDRICKSON, M.D., ROBERT I. LEVY, M.D., AND ROBERT S. LEES, M.D. of Bethesda, MD.

Great news: entire pentology is free for downloading:

<http://profiles.nlm.nih.gov/FF/Views/Exhibit/documents/scientist.html> Once there click on: Fredrickson, Donald S., Robert I. Levy, and Robert S. Lees. "Fat Transport in Lipoproteins--An Integrated Approach to Mechanisms and Disorders." *New England Journal of Medicine*, (1967): Article.

To be totally honest, the lipoproteins classification first appeared in an editorial in Circulation, entitled "A System for Phenotyping Hyperlipoproteinemia" Circ. 1965;31:325-327 authors: Fredrickson and Lees. The pentology was a much more detailed discussion. To put things in perspective: I wonder if the NEJM has ever since published a 5 part series on any disease?

In the paper they correctly claimed: with the exception of free fatty acid concentrations which have no lipoprotein equivalents, all abnormalities on plasma lipid concentrations can be translated into dyslipoproteinemia. The shift of emphasis to lipoproteins offers distinct advantages in the recognition and management of such disorders. SO - TO ALL WHO ARE STILL STUCK IN THE LIID ERA, GET OVER IT! The lipid era ended and the lipoprotein era began in 1967. Tragically there are still those running around thinking they can diagnosis lipoprotein disorders and CV risk by analyzing lipids. By the way in the paper, they actually discussed the reason for calling the science Lipidology and physicians who master that science, Lipidologists is that it is simply too cumbersome to say Lipoproteinology and Lipoproteinologists! However, to be factual, all certified by ABCL are lipoproteinologists! STOP THE LIPID PROFILES - NMRs and apoB for all! The lipid era ended in 1967. At least the ADA/ACC and AACC in their recent position statements of 2008 and 2009 agree. Let's hope the NCEP crowd reads the 1967 pentology.

The paper is packed full of so many delicious tidbits and no one should be certified in Lipidology without reading it. How you really know where you are without revisiting from where we came. I want you to think about the follow statement they made, which is even truer today than it was then: " A and B proteins are the primary components of the lipoproteins. In plasma they usually occur with predictable complements of lipid that feature differing proportions of cholesterol and phospholipids. When glycerides appear in quantity these 2 lipoproteins become involved with its transport. Glyceride thus becomes the third and most dynamic factor in determining the nature of the lipoprotein distribution in plasma.

Translation: The apoB (beta) and apoA (alpha) lipoproteins traffic cholesterol, phospholipids and (as they were called then) glycerides. The only lipid concentration that changes throughout the day is TG. Thus TG run the show and are by far the most important (dynamic) factor regulating lipoproteins. MY GUESS IS ABOUT 80-90% OF PRACTICING CLINICIANS DO NOT KNOW THAT. Thus TG remains the forgotten and disrespected lipid.

ENOUGH! Let's get back to **lipoproteinology**:

I was asked about a 46 year old patient with morbid obesity (383 lb). He has hypertension, DM, and allergies, as well as osteoarthritis knees and ankles. He is on multiple medications for his blood pressure, and metformin and Levimir for his Diabetes. He is also on aspirin and prn naproxen. He has a family history of DM and hypertension, but not atherosclerosis that he is aware of. He is on no lipid medications.

Lipid Profile:

TC = 121 mg/dL TG = 107 HDL-C = 29 mg/dL LDL-C = 71 mg/dL hs-CRP = 4.73

The provider states: "Given his history of DM, high BP, and elevated CRP, I think he should be on a statin, but his TG and total/LDL/non-HDL are all pretty enviable numbers. Should I use a statin, and what am I aiming for on targets. I suspect that the Jupiter trial has some applicability, given its focus on CRP and good outcomes with Crestor. I find it interesting that although he meets the criteria for metabolic syndrome, he has good TG."

DAYSRING DISCUSSION:

This is a perfect case to discuss after what I have written above. However this case cannot be discussed without, of course analyzing lipoproteins. First, one does not have to have hypertriglyceridemia (at least using 150 mg/dL as a cutpoint) to be a metabolic syndrome. It is

only one of five criteria. Many severely IR patients do not have TG of > 150 mg/dL. There are patients with TG of 70-130 mg/dL who are significantly insulin resistant and who qualify for the syndrome using other criteria.

Let's pretend we are still way back in the lipid era: As noted the patient is at NCEP ATP-III LDL-C and non-HDL-C goals of therapy (although technically there is no non-HDL-C goal when TG are < 200 mg/dL) and thus technically he does not qualify for Rx using 2001 and 2004 NCEP criteria. The ADA just issued its new 2010 Standards of Care paper for diabetes and under the dyslipidemia management section states: statin therapy should be added to lifestyle for all diabetics without overt CVD who are over the age of 40 and have one or more CVD risk factors (which this man certainly does). Diabetes Care 2010;32:(suppl1):S33-S61).

Earlier last year however the American Association of Clinical Chemists or AACC (lab pathologists organization) issued a position statement (Clinical Chemistry 2009;555:407-419) that non-HDL-C goals should be determined by not adding 30 mg/dL (a normal VLDL-C as defined by 2001 NCEP) to the LDL-C but rather 15 mg/dL (as they believe a normal TG is < 75 and thus a normal VLDL-C would be 15 as VLDL-C = TG/5). If we consider this patient to be very high risk, his non HDL-C goal using AACC criteria is 70 + 15 or 85 mg/dL. The patient has a non-HDL-C of 92 (slightly high). The Amer Journal Cardiology (2009;104:1393-97) just published data that in men, if the TG/HDL-C ratio is > 3.0, there is almost a doubling of CV risk independent of LDL-C. This patient's TG/HDL-C ratio is 3.6. So my bet is with his morbid obesity, diabetes, high TG/HDL-C ratio, high non-HDL-C your patient is an MI waiting to happen. To really understand the problem: keep reading.

The ADA/ACC like the AACC also issued a recent consensus statement that lipid parameters are no longer reliable in patients with cardiometabolic risk because even in patients with normal LDL-C and non-HDL-C there is moderate discordance with apoB or LDL-P. The morbid obesity, hypertension, diabetes and elevated CRP clearly support severe insulin resistance and severe cardiometabolic risk. In such patients they state that pharmacological decisions cannot be made without first ordering atherogenic particle counts using either apolipoprotein B and the NMR determined LDL-P measurements. My guess is because of the high TG of 107 (a physiologic TG is 10 to 70 mg/dL with a mean of 30 mg/dL), there is excess CETP activity which transfers TG from VLDLs to his HDLs and LDLs. Those particles become both TG-rich and very cholesterol depleted. Ultimately they become small and dense and the HDL dissociates and its apoA-I is excreted (explaining the very low HDL-C). Since it takes many more cholesterol depleted LDLs to traffic a given level of LDL-C, patients can have very high LDL-P levels with a perfect LDL-C. This patient's LDL-C looks OK but his LDL-P (a much more important risk factor) is likely very elevated. Remember Tim Russert died with a similar LDL-C of 68 mg/dL.

One needs to order apoB or the NMR test through Labcorp or LipoScience (www.lipoprofile.com). Of course if the LDL-P is high, he will need a statin or statin plus whatever else it takes to get to goal. As mentioned above, the ADA would want him on a statin. In addition to a statin, I would use 1000 mg of N-3 FA (Lovaza), but that will not help the lipoproteins. If one checked the Omega 3 index test I suspect he would be very deficient in N-3 FA. One last thought: clearly bariatric surgery might well eradicate or vastly improve his diabetes, insulin resistance and suspected lipoprotein abnormalities.