

## Dr. Underberg

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**From:** TDayspring@aol.com  
**Sent:** Sunday, June 19, 2005 3:52 PM  
**To:** TDayspring@aol.com  
**Subject:** Lipidaholics Weekly: Lipid Case # 140 Treating patients with abnormal LFTs

Good Day Lipidaholics: Some great news: A recent post-hoc analysis of the PROVE IT trial (atorvastatin 80 mg vs Pravastatin 40 mg) revealed that the lipid profile response to either statin was considerably better in the summer months than during winter. Well summer is upon us so look for great responses in your patients. So maybe we can help the patient I was consulted about.

51 year old obese, well-controlled, type 2 diabetic with a history of Hepatitis C, former alcoholism, who has an A1c of 6.3% on multiple daily insulin injections. He has treated hypertension and no significant family history.

Labs: no microalbuminuria, liver enzymes that are twice normal,

TC = 138, TG = 216, HDL-C = 34 LDL-C = 61,  
 Non-HDL cholesterol 104 TC/HDL-C = 4.05 TG/HDL-C = 6.5  
 NMR LipoProfile  
 LDL particle number (LDL-P) = 1511,  
 LDL size 19, (small, Pattern B)  
 Large HDL 6 (desirable > 30)  
 Large VLDL 50 (desirable < 7)

This gentleman is chronically maintained on TriCor 145 qd, fish oil, d-alpha tocopherol, and garlic. He has been unsuccessful with nutritionalist-guided diets in the past.

I was asked: Would you have expected his LDL particle number to have been so high? Would the triglycerides and HDL cholesterol levels have been predictive (noting the normal non-HDL cholesterol)? Would you add Zetia alone (considering the hepatitis history and enzymes twice normal), or would you jump on a low dose water-soluble statin also?

### DAYSRING ANALYSIS

This is a perfect example of a normal LDL-C and non HDL-C level in a patient who still has multiple lipoprotein abnormalities. In the PROVE-IT trial, a mean LDL-C of 62 mg/dL was achieved in the atorvastatin (Lipitor) arm and yet 25% of patients on atorva had an event. Lipitor 80 mg had no superiority over Pravachol 40 mg in these with an HDL-C < 40 or whose baseline LDL-C was < 120 mg/dL. The 2005 ADA Lipid Guidelines suggests starting Type 2 diabetics aged >40 to start a statin if TC is > 135 mg/dL (LDL-C in such patients is likely 70-80 mg.dL). NCEP 2004 addendum gives clinicians an option to start all high risk persons on a statin if LDL-C is < 100 mg/dL. Did you ever wonder why guidelines want you to treat higher risk patients (like type 2 diabetics) who already have an LDL-C at goal? The answer is that these patients, despite their normal LDL-C have increased apoB or LDL-P (the best lipid risk factors seen in multiple trials).

I always implore to my followers, students and audiences to stop betting lives in high risk patients by making predictions based on lipid concentrations. The only way atherogenic lipids (sterols) enter the artery wall is as passengers in lipoproteins. Our best gauge of risk (diagnostic cardiology) is looking for abnormal lipoproteins and our best therapies (therapeutic cardiology) successfully modulate lipoproteins.

It is mind boggling that almost all physicians think NCEP has targets of therapy specific to concentrations of LDL-C, HDL-C and TG. In fact NCEP sets no TG OR HDL-C LEVEL AS A GOAL OF THERAPY. I tease clinicians that if a PHARMA rep (or heaven forbid a speaker) ever tells them NCEP wants them to raise HDL-C or dropping TG to any specific level to throw them out of your office. You may quote from the executive summary of NCEP published in JAMA 2001;285:2486-2497:

**The primary aim of therapy is to achieve the target goal for LDL cholesterol. When triglycerides are**

**borderline high (150-199 mg/dL), emphasis should also be placed on weight reduction and increased physical activity. For high triglycerides (200-499 mg/dL), non-HDL cholesterol becomes a secondary target of therapy.**

**Low HDL cholesterol both modifies the goal for LDL-lowering therapy and is used as a risk factor to estimate 10-year risk for CHD. ATP III does not specify a goal for HDL raising. Although clinical trial results suggest that raising HDL will reduce risk, the evidence is insufficient to specify a goal of therapy. In all persons with low HDL cholesterol, the primary target of therapy is LDL cholesterol; ATP III guidelines should be followed to achieve the LDL cholesterol goal. Second, after the LDL goal has been reached, emphasis shifts to weight reduction and increased physical activity (when the metabolic syndrome is present). When a low HDL cholesterol is associated with high triglycerides (200-499 mg/dL), secondary priority goes to achieving the non-HDL cholesterol goal, as outlined earlier.**

I am frequently amazed at how many small LDL particles can exist in patients with very nice LDL-C and non HDL-C. The LDL size of 19 nm in this patient is incredibly small. Particle diameter has immense consequences at any given LDL-C levels. Clinicians often forget or do not know that the volume of a sphere (particle) varies by the third power of the radius. Thus for particles varying by 3 nm (19 vs 22), there will be 40% less cholesterol in the smaller particle or said another way it will take 40-70% more particles for a 19 nm LDL particle to transport the same amount of cholesterol as a 22 nm LDL particle. This is such a crucial point and totally explains the disconnect in risk between Lipid and Lipoprotein concentrations. Thus, the sooner we start doing particle concentrations rather than cholesterol measurements, the more lives we will save. In essence CV risk and goals of therapy come down to apoB or LDL-P. Apo is available in any lab in America (not often reimbursed) and LDL-P is only available in the NMR LipoProfile ([www.lipoprofile.com](http://www.lipoprofile.com)). PLEASE NOT THAT NO OTHER (available) ADVANCED TESTING TECHNIQUE CAN QUANTITATE LIPOPROTEINS, and those techniques bring nothing (but expense) to the diagnostic thought process.

Back to the patient at hand: Your only suspicion of danger in looking at the lipid profile in this high risk patient (because of the type 2 diabetes) is the high TG accompanied by what I believe to be a slightly increased TC/HDL-C and a grossly abnormal TG/HDL-C ratio. Both of the latter (especially when LDL-C is fine) are clues that a patient has small LDL particles. So even though you strongly suspect a patient has small particles, how can you possibly guess whether the LDL-P (apoB) is elevated. It is very tough if not impossible to guess exactly how small the particles are and that is what will determine how many are necessary to transport the 61 mg of cholesterol present in the LDL particles per dL of plasma.

**The VLDL-C is a clue.** The VLDL-C in this patient is TG/5 or 216/5 or 53 mg/dL ( $n < 30$  mg/dL). NCEP suggest that we use VLDL-C as an indication or atherogenic remnant apoB containing lipoproteins. In other words if VLDL-C is up, Non HDL-C (TC minus HDL-C or VLDL-C plus LDL-C) is probably elevated and Non HDL-C is the best lipid predictor of apoB when TG are high. If apoB is up, LDL-P has to be elevated as 90% of apoB particles (because of their long half life) are LDL particles.

**The low HDL-C is also a clue.** Until proven otherwise, in drug naive patients, low HDL-C is almost always associated with elevated apoB. TG from VLDL are swapped for cholesterol within HDL by CETP (cholesteryl ester transfer protein). The resultant TG-rich cholesterol-poor HDL are remodeled by hepatic lipase creating small HDL, which are subject to renal excretion because of their small size. Thus people with high apoB (too many apoB remnants and small LDL) will lack HDL particles, especially the large ones. Thus, much of the risk associated with low HDL-C is their association with increased numbers of atherogenic TG-rich apoB particles (remnants and small LDL). ALSO NOTE THAT THIS DOES NOT MEAN LARGE HDL PARTICLES ARE GOOD AND SMALL ONES ARE NOT. The lack of large HDL is virtually always associated with too many small apoB containing LDL particles. That is why initial therapy must be directed at apoB, rather than HDL-C. All HDL particles are needed for the proper transport of cholesterol to and from the liver, endocrine glands and other tissues.

In this case, the non HDL-C of 104 is considered fine in all but very high risk patients. This patient does not fall into NCEP's optional very high risk category or does he? In actuality it is very debatable. If the BP in a diabetic is not controlled or he smokes he would qualify, if the BP is controlled or he does not smoke he does not.

Keep in mind that ADA and NCEP suggests a type 2 diabetic be treated even if LDL-C seems fine. No matter what the baseline LDL-C, they suggest a reduction of at least 30%. Thus NCEP and ADA suggests this patient

would have less future risk if the LDL-C was 41 mg/dL (30% of 61 is 20:  $61 - 20 = 41$ ). A physiologic LDL-C level is 10-40 mg.

Now: what do in this complicated, high CV risk patient with active liver disease. All statin package inserts state that the drugs are contraindicated in patients with active liver disease or with unexplained persistent elevations of transaminases. Neither Zetia nor WelChol is contraindicated in the presence of elevated aminases although one is warned to balance risk vs benefit if hepatic insufficiency is present. All fibrates carry the contraindication for use warning if hepatic dysfunction or unexplained aminase elevation is present.

An important question is are the LFTs due to the hepatitis C or to steatohepatitis or both? recent studies have revealed that the presence of fatty liver is highly associated with insulin resistance and the metabolic syndrome as well as the presence of atherosclerosis (carotid). Increasingly, although technically contraindicated by package inserts there is little hesitation in writing lipid-lowering drugs in patients with active fatty liver as opposed to other liver diseases.

NCEP ATP III states that it has not been determined that statin aminase elevation constitutes true hepatotoxicity. Progression to liver failure, if it ever occurs, is exceedingly rare. It is not know whether statins worsen the outcomes in persons with chronic aminase elevations due to hepatic C or B. There is no evidence that they are harmful in patients with fatty liver due to obesity. Their use in persons with various forms of chronic liver disease depends on clinical judgement that balances proven risk vs benefit.

Apropos of this discussion is a just published article on statins and aminase elevation by Charles E. et al. in the American Journal of Medicine (2005) 118, 618–624: The article notes:  
*"The elevation of liver enzymes observed in the clinical trials may actually be related to cholesterol-lowering per se rather than a direct hepatotoxic effect of statins. Cholesterol lowering may increase hepatocyte membrane permeability, resulting in an increase in liver enzyme leakage. Animal toxicology data and the fact that liver enzyme elevation has been reported with other classes of cholesterol lowering medications support this theory."*

The best way to reduce the elevated LDL particle number is to upregulate hepatic LDL receptors. The drugs that do this are statins, ezetimibe (Zetia) and bile acid sequestrants (with WelChol being the modern day sequestrant of choice) and plant stanols (Benecol). I do not recommend plant sterols due to their potential atherogenicity. WelChol, a polymer is not as TG aggravating as the bile acid sequestrants which are resins (cholestyramine or colestipol).

In view of the active liver disease one could start Zetia 10 mg daily with Benecol Chews (4/day). WelChol is another option or you could use al three, but the Zetia and Benecol must be dosed 2 hours before or 4 hours after the WelChol. I am not optimistic that these therapies can normalize the LDL-P

If I knew the hepatitis C was stable and not in a period of decompensation **I would go** with a hydrophilic statin with a long history of liver safety, pravastatin. Keep in mind the package insert would state that Pravachol is contraindicated in this patient, yet Pravachol is the only statin which the FDA does not mandate hepatic follow up testing, although in this patient LFTs should be followed. It is likely LDL-C goal (who really knows about LDL-P goal) will be achieved with Pravachol in this patient. If Pravachol did not then Crestor (rosuvastatin) 5 mg (hydrophilic) or Vytorin 10 mg would be an option. Vytorin contains the lipophilic simvastatin (Zocor), but the 10 mg dose is quite safe and not likely to aggravate the liver.

It is possible that upregulation of LDL receptors with statins or stain/ezetimibe would be incapable of totally normalizing LDL-P, as LDL receptors have a harder time attaching to and removing small rather than large LDL particles from plasma. ApoB is conformed differently on small particles in ways that may not be recognized by the LDL receptor. In such patients shifting LDL particle size can significantly improve the statins ability to remove LDL particles. So if achieving LDL-P goal did not occur with the above therapies, then the addition of fenofibrate (TriCor 145 mg) or Niaspan (in titrated fashion) become options. Because of the insulin dependent diabetes, Niaspan becomes a drug of last resort. One would use it only if the other options were ineffective, not tolerated or aggravated the liver.

Nonetheless in today's medicolegal world where sharks are always watching, most non lipidologist clinicians would be unlikely to add a fibrate or Niaspan to a statin in this patient. To bad, because if the aminase elevation is solely fatty liver, aggressive lipid intervention might help it.

It would be silly not to use a statin, but if the patient, adamantly refused it, I would then suggest a TriCor/Zetia and Benecol combination. Not long ago a trial in 600 patients demonstrated nice synergistic lipid benefits with excellent tolerability (European Heart Journal Publish-Ahead-of-Print published March 21, 2005). Unlike gemfibrozil, which interferes with glucuronidation of ezetimibe, there is no major pharmacokinetic interactions between fenofibrate and ezetimibe (CURRENT MEDICAL RESEARCH AND OPINION 2004;20:1197–1207).

## REFERENCES OF THE WEEK

1) An Editorial Update: Should She Take Aspirin? *Annals Int Med* 2005;142:942 High-quality evidence shows that 100 mg of aspirin taken every other day has little or no effect on all-cause mortality but does reduce the risk for stroke in healthy middle-aged and elder women; evidence on heart disease is less clear. Smoking might antagonize the potential benefits of aspirin. Women older than 65 years of age (presumably with higher baseline risk for cardiovascular disease) may benefit more from aspirin than younger women.

2) Enhancing reverse cholesterol transport: the case for phosphatidylcholine therapy  
Editorial by Henry Pownall and Christian Einholm: *Current Opinion in Lipidology* 2005, 16:265–268. Every one is touting recombinant HDL which will almost never come to market and forget that since 1975 we have had evidence that IV lecithin is all we need!

3) Weight Loss–Associated Induction of Peroxisome Proliferator–Activated Receptor-alpha & Peroxisome Proliferator–Activated Receptor-gamma Correlate With Reduced Atherosclerosis and Improved Cardiovascular Function in Obese Insulin-Resistant Mice. **With PPAR alpha/gamma drugs around the corner (Muraglitazone with the brand name of Pargluva from BMS) this is very interesting reading.**  
Conclusions—Induction of PPAR alpha and gamma in adipose tissue, heart, and aortic arch is a key mechanism for reducing atherosclerosis and improving cardiovascular function resulting from weight loss. Improved lipid metabolism and insulin signaling is associated with decreased tissue deposition of oxidized LDL that increases cardiovascular risk in persons with the metabolic syndrome. (*Circulation*. 2004;110:3259-3269.)

4) Effect of Pravastatin on Cardiovascular Events in People With Chronic Kidney Disease Conclusions—Pravastatin reduces cardiovascular event rates in people with or at risk for coronary disease and concomitant moderate CKD, many of whom have serum creatinine levels within the normal range. Given the high risk associated with CKD, the absolute benefit that resulted from use of pravastatin was greater than in those with normal renal function.  
(*Circulation*. 2004;110:1557-1563.)

5) Comparison of rosuvastatin and atorvastatin for lipid lowering in patients with type 2 diabetes mellitus: results from the URANUS study *Cardiovascular Diabetology* 2005, 4:7 Conclusions: Conclusion: At the start dose and following dose titration, rosuvastatin was significantly more effective than atorvastatin at reducing LDL-C and achieving European LDL-C goals in patients with type 2 diabetes. **TD VIEW:** This is major continued evidence that Crestor is far and away the most potent statin in modulating lipoproteins.

6) Dyslipidaemia among Indo-Asians strategies for identification and management. *Br J Diabetes Vasc Dis* 2005;5:81–90 Indo-Asians have the highest rates of coronary artery disease CAD) despite the fact that nearly half are lifelong vegetarians.

## DAYSPRING TRAVELS (next few months)

Brick, Summit, NJ  
Dallas, Forth Worth, Austin, THIS WEEK  
Houston, TX  
Oxnard, Santa Monica, Bakersfield, Tarzana, CA  
Atlanta, Roswell, GA and surrounding areas  
Little Rock, AR  
Richmond, VA  
Wilmington, Charlotte, NC  
Omaha, NE  
Pikesville, MD  
Newark, DE  
West Chester, PA

Gadsden, AL  
Chattanooga, Knoxville, Nashville, TN  
Albany, NY  
Charleston and Columbia, SC  
Finally a return to Charleston and Beckly WV

Reminder: My previous cases of the week discussions can be reviewed and downloaded in PDF form at <http://www.nypcvs.org/pages/1/index.htm>

I contributed to a nice discussion on interpreting the NMR LipoProfile at <http://www.sjhg.org/> Click on Hearbeat icon and download May 2005. I have attached the pdf to this e-mail

Remember the National Lipid Association [www.lipid.org](http://www.lipid.org) Join: The new syllabus on Metabolic syndrome is ready for release. **Be sure to attend the annual meeting this summer (July) in Chicago.** They are offering a Masters Course for those ready to take that plunge. On line registration is now available. I will be there.

North American Menopause Society [www.menopause.org](http://www.menopause.org) Become a certified menopause practitioner!

WANT MY SLIDES? Two CME CDs are available for free. You get my animated slides, my voice and slide notes. (1) Understanding the Influence of Triglycerides on Lipid and Lipoprotein Pathobiology" and (2) Treatment considerations form TG-rich Lipoprotein Pathobiology" The slides are very much worth the price: FREE! Do the Lipoprotein Physiology one first. It is essential to understand the basics before looking at the one dealing with treatments.

If you would like both CDs, [FAX a request to ACCESS Medical Group Department of Continuing Medical Education at 847-392-2257](#) Request both CDs. If your fax goes unanswered you should contact Susan Pazderski at Access Medical, (847) 392-2227.

I find it difficult to come up with new or original accolades when talking about our servicemen and women. Their daily sacrifices are mostly beyond comprehension for the average non-veteran citizen. Just thank your lucky stars, as do I that our country has always had such dedicated pros. a robust Thank You to them and their families.

Happy lipiding and may the particles be with you,

Tom

Thomas Dayspring, MD, FACP  
North Jersey Institute of Menopausal Lipidology  
516 Hamburg Turnpike  
Wayne, NJ 07470  
Tel: 973-790-8604  
Fax: 973-790-1488