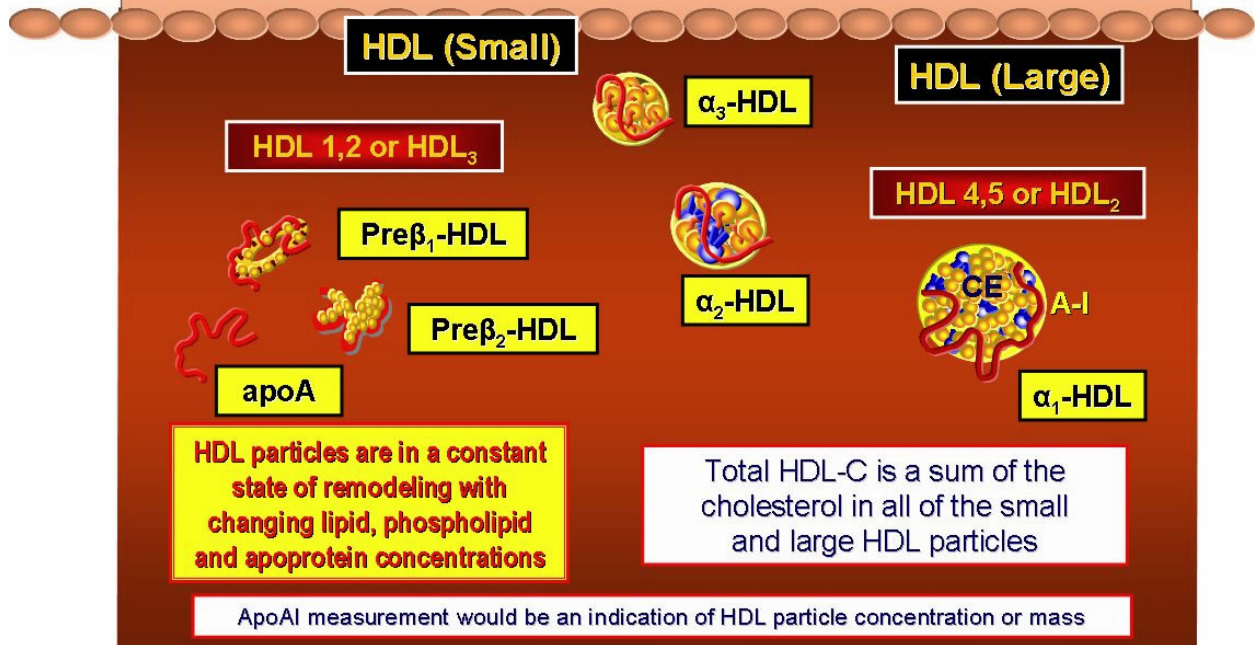


Total HDL-cholesterol Levels



I have been asked to clear up what drugs do to HDL particles and HDL-C. This is a rapidly changing field.

Does it really matter what a drug does to HDL subparticles? The lipid wars have become so competitive, certain drugs are being marketed as having some HDL subparticle benefit. Any rep trying to sell their product by discussing HDL subparticles is in way over their head and is almost certainly not thoroughly schooled on this topic.

Since many practitioners are now doing advanced lipoprotein testing, they are obtaining and observing HDL particle baseline and follow up data. Many do not know what to do with such data. Much of the confusion comes from the statement from LipoScience that Niacin increases large HDL more than other therapies. That is a very true statement. However, somehow lost in that statement is that neither LipoScience nor any governing body nor the FDA recommends HDL particles be a goal of therapy. LipoScience properly states (based on good data) that at baseline (in patients not on drugs) the lack of large HDL particles is a risk factor highly correlated with insulin resistance, small LDL and VLDL remnants. These patients have increased TG which initially makes the HDL large particles TG-rich and cholesterol poor. The lipolytic action of hepatic lipase hydrolyzes (removes) TG and rapidly changes these large particles to small HDL: this causes a reduced amount of large HDL on the NMR test and decreased HDL-C on conventional testing. When one treats at risk patients with low HDL-C, the NCEP suggested target of therapy is not to raise HDL-C or HDL subparticles to some magical level, but rather, to reduce LDL-C and Non HDL-C: in other words one should lower apoB in patients with low HDL-C. NCEP makes no recommendations that one should attempt to make HDL particles large!

NCEP and most experts will tell you that fractionation of HDL is not recommended at this time and has little role in clinical practice as far as determining the efficacy of a drug. That being said, different drugs do different things to HDL-C and HDL subparticles. If a clinician is following HDL particles on follow up testing (NMR) the clinician better do some serious reading and develop a thorough understanding of the

topic. Reverse cholesterol transport is a very complicated, dynamic flux process that cannot be predicted from HDL-C levels or subparticle determination. Believe it or not studies demonstrate one can lower TG, lower apoB and reduce outcomes and in the process make HDL either large or small. It will depend on the particular therapy used. Bottom line is that CV risk reduction can occur independent of what happens to HDL particles.

To give you an idea how the complexity of HDL subparticles, please read on. The process of reverse cholesterol transport (RCT) is a flux process that involves many "players" some of which (to name just a few) include PPAR alpha, gamma and delta, hepatic, lipoprotein and endothelial lipase, LCAT, cholesteryl ester transfer protein, phospholipid transfer protein, scavenger receptors B1, CD-36, ABCA1 transporters, Liver X receptors, sterol regulatory element binding proteins, hepatic and intestinal apoA1, other apolipoproteins, cubilin and megalin, and LDL receptors.

If assembled properly, **all** HDL particles (big and small) are beneficial. There is this absurd belief being promulgated that only big HDL particles are beneficial. Patients with apoA1 Milano have very small HDL particles, very low HDL-C and yet do not have CHD risk. They have very efficient RCT. Japanese women with CETP disorders have very large HDL particles and very high HDL-C levels, yet the particles are dysfunctional, impairing RCT and the elevated HDL-C is associated with CV risk.

Maybe we would be better off looking at apoA1 measurements as the best way to judge therapy. ApoA1 is the surface apoprotein on HDL particles and its measurement is an indicator of total HDL mass or particle concentration. . As apoA1 levels increase, HDL particle numbers increase. There are several studies (epidemiological and clinical trial) that have determined the usefulness of apoA levels at baseline and as a predictor of therapy (See AFCAPS, AMORIS).

There are four ways to increase apoA: Note that one can raise apoA without dramatically raising HDL-C levels: (see gemfibrozil in VA-HIT). Also one can raise HDL-C without elevating apoA as in the case of resins: they increase HDL-C via an LXR induction of ABCA1 which will facilitate delipidation of foam cell cholesterol to apoA (small or pre-beta HDL) particles. There is no major increase in apoA.

1) Induce hepatic production, Fibrates do this through PPAR alpha. Estrogen does it through estrogen receptor agonism. Statins may do it through an associated PPAR alpha effect. Other drugs can also have an effect: dilantin, TZDs.

2) Induce lipolysis (TG removal) of apoA containing chylomicrons. ApoA will break away from the chylomicron. Anything that increases lipoprotein lipase will do that. Fibrates are the best agents for that (another PPAR alpha effect). Statins induce LPL to variable degrees.

3) Downregulate hepatic SRBI (HDL receptor) preventing delipidation of large HDL particles. Estrogen does this. The HDL particle will not be able deliver cholesterol to the liver.

4) Downregulate the hepatic HDL "holo-particle" or catabolism receptor. Niacin is the only drug that does this. Without that receptor, large HDL particles cannot undergo hepatic endocytosis and thus they stay in the plasma. In effect this prevents catabolism of apoA HDL particles (raising apoA and HDL-C). However if large particles are no longer endocytosed, reduced amounts of cholesterol is getting to the liver.

What HDL subparticle data do we have from trials:

In the VA-HIT, gemfibrozil there was an increase in apoA and small HDL particles. This was tied into event reduction. If one understands how fibrates work, one would know that the number of small HDL has to increase. Fibrates increase apoA (from liver and chylomicrons): Fibrates help upregulate ABCA1 transporters in tissue and foam cells, causing lipidation of apoA, creating transient large HDL particles. Such large HDL particles are immediately delipidated (and made small) at the liver by SRBI (upregulated by fibrates). Large HDL can also be made small by the action of plasma CETP, which transfers cholesteryl ester from large HDL to apoB particles (LDL and VLDL) in return for TG. The resulting large

HDL is now TG rich and undergoes lipolysis by hepatic lipase creating small HDL particles. In the one study I am aware of TriCor (fenofibrate) has been shown to increase mostly small but also large HDL

So although fibrates are efficiently enhancing RCT via HDL flux, small HDL will be the resultant and predominant particle in patients on fibrates. This is highly desirable as small HDL (lipid free or lipid-poor apoA) is the only particle that can enter the arterial wall to initiate the RCT process. And most of all, this was an important MOA of the fibrate in the VA-HIT.

In HATS (successful, angiographic trial using Zocor and Slo-Niacin) the niacin and the statin caused an increase in large HDL and a reduction in small HDL. This is exactly what should happen if one understands what statins and niacin do to HDL particles. Niacin does not increase apoA production. Statins have an ability to do increase apoA1 (their PPAR alpha effect is due to inhibited prenylation of rho and ras. Crestor is by far the most powerful and Lipitor the weakest on apoA). There is some recent evidence that niacin by increasing prostaglandin D2 which has PPAR gamma effect which upregulates ABCA1 lipidation of apoA (creating large HDL). Once the HDL particles are lipidated (acquire cholesterol) and made large, the HDL particles will tend to stay large on statins and niacin

1) Statins have some inhibitory effect on CETP, which will prevent transfer of cholesteryl ester from large HDL to apoB particles. Statins also can have an inhibitory effect on hepatic lipase (an enzyme that enhances HDL particle lipolysis). Both of these effects will keep HDL particles large. Keep in mind that patients who have large HDL particles due to CETP deficiency have very large HDL particles that are dysfunctional and do not contribute to HDL flux. So no one truly knows if it is good that statins can increase HDL size.

2) Niacin inhibits hepatic lipase. This also will prevent lipolysis (TG removal) of large HDL. However, there is evidence that if large HDL does not undergo some modification from hepatic lipase, the HDL particle cannot attach to hepatic SRBI which would impair hepatic delipidation of the HDL particle (in effect inhibiting delivery of HDL cholesterol to the liver). Niacin also downregulates the hepatic HDL "holo-particle" or catabolism receptor (a receptor that performs endocytosis of large HDL particles). The effect is that HDL particles and their cholesterol load are not getting into the liver. It is possible RCT could occur if the large HDL particles created by niacin could transfer the cholesterol to apoB using CETP: but that would create small HDL particles which does not seem to happen on niacin. It is likely that the delayed catabolism of large HDL allows the HDL particle to stay in the plasma and perform many other antiatherogenic functions (anti-inflammatory). Note that if HDL particles stay large, they cannot reenter the arterial wall and initiate or perform further RCT. Only small particles can do that. In effect niacin increases HDL-C and apoA by delaying the catabolism of large HDL particles.

Bottom line: If you use a fibrate expect small HDL particles and apoA to increase. The HDL-C increase is very variable and will mostly be related to the baseline TG and HDL-C level: (the higher TG level and the lower the HDL-C at baseline, the more will be the fibrate induced HDL-C rise). Multiple trials have demonstrated that fibrates reduce clinical events. If one prescribes a fibrate and is doing NMR followup, never stop the fibrate because small HDL is increasing and large HDL is not increasing. The apoB particles (LDL and VLDL) will reduce in number and become less atherogenic.

If you use niacin, there will be an increase in large HDL particles, apoA and HDL-C. One prospective, empowered trial exists showing that niacin by itself reduces clinical events: the Coronary Drug project from which there is very little HDL data and no HDL particle data. Niacin through its inhibitory effect on TG synthesis (inhibition of hormone sensitive lipase and DGAT2) lowers apoB. Like fibrates Niacin lowers atherogenic apoB.

Statins work and as monotherapy they do variably increase HDL-C, apoA and it is irrelevant what they do to HDL particles. Statins work because they significantly lower apoB.

Guess what: Statins, fibrates and niacin work very well in reducing CV events and have similar outcome reductions. So it is not important to the average clinician what they do to HDL subparticles. But please do not be hoodwinked by reps on this topic of how important it is to affect HDL size. It has no

comparative meaning that niacin increases HDL size and fibrates do not. Be happy if a patient on niacin develops large HDL and be very happy if on a fibrate the n number of small HDL increases. Never stop a fibrate because the number of large HDL decreases and the number of small HDL increases. LISTEN VERY CAUTIOUSLY WHEN BEING DETAILED ON THIS TOPIC by people from Pharma and from many speakers who are in way over their heads on this topic.

Now go take an ADVIL for the headache I just caused.

DAYSRING TRAVELS over June and July

Edgewater, Parsippany, Clinton, Voorhees and Morristown, NJ
Manhattan, Staten Island
Westport, CT
Greensboro, NC Raleigh, NC
Reheboth Beach, DE
Owensboro, KY
Evansville and Terre Haute, IN
Atlanta, GA
Southfield and Jackson, MI
Wichita and Kansas City, KS
Des Moines, IA
Columbia, Charleston and Beaufort, SC

Has everyone signed up for the National Lipid Association Annual Meeting in Orlando August 5th to 8th. See you there!

References of the Week

Prayers to the troops and a special prayer and last good-bye to the 39th President of the United States, Ronald Wilson Reagan! We will not see his like again.

Regards and happy lipiding,

TD

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