Lipid/Lipoprotein Disorder Treatment Algorithm

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Here is my algorithm (updated 2011) on how to choose specific lipid/lipoprotein-modulating drugs to achieve lipid/lipoprotein goals, with the given being that since atherosclerosis is an apolipoprotein B (apoB) mediated disease it is the lipoprotein goals (not the lipid concentration goals) that really matter. Adding complexity to atherosclerosis is that the apoA-I (HDL particles) may impact clinical events positively if clinicians can increase their number (total HDL-P) as well as improving their CV functionality (of which no marker currently available). Because HDLs can carry several apoA-I proteins, apoA-I is at best an estimate of total HDL-P (i.e. it can be discordant with total HDL-P). At this time the only seriously validated by clinical trial data, measurements of LDL-P and HDL-P are those obtained using NMR spectroscopy (LipoScience) or measured (never calculated) apoB. Unlike LDL-P by NMR, other methodologies that measure LDL-P have not been validated in large clinical trials. Although LDL and HDL sizes and subspecies concentration can serve as markers of insulin resistance, they are not goals of therapy. Once you have total LDL-P, none of the subparticle measurements have any statistical relationship to CHD risk. Those guidelines not yet advocating apoB or LDL-P testing use non-HDL-C as their LDL-P surrogate (not LDL-C by itself). There is no specific TG or HDL-C goal of therapy in NCEP ATP-III.

There are two treatment algorithm pathways depending if the TG are > or < than 500 mg/dL. The first therapeutic mission if TG are < 500 mg/dL is almost always to reduce the number of apoB particles from plasma. Of course in the vast majority of dyslipoproteinemic or hyperlipoproteinemic patients 90-95% of the apoB particles are LDL particles. Only in the much rarer Fredrickson Type I, Type III, some Type IVs (those with Familial Hypertriglyceridemia) and Type Vs lipoprotein disorders where LDL particles not the predominant species (all of those phenotypes are characterized by severe hypertriglyceridemia in which chylomicrons, VLDLs or IDLs are the particles at play). Familial hypercholesterolemia (FH) and familial combined hypercholesterolemia (FCHL) are LDL particle disorders.

In those with too many LDL particles, LDL-P can be lowered by upregulating LDL receptors (LDLr) to remove apoB particles (enhancing clearance) from plasma and/or reducing production of apoB particles. The best way to enhance apoB particle clearance via LDLr upregulation using monotherapy in order of potency is statin (dose dependent) or ezetimibe or bile acid sequestrant (colesevelam) or plant stanol. Using combinations of those meds will further upregulate LDLr. Raloxifene (Evista) also upregulates LDLr and lowers apoB in the 12-15% range (off-label use).

ApoB can also be lowered by decreasing hepatic production of VLDL particles (some of which are the predecessors of the LDLs). Reducing VLDL-P production at the present time can only be accomplished by reducing lipid substrate (free cholesterol or cholesteryl ester and TG) in the liver. Statins, by lowering hepatic cholesterol synthesis, do reduce apoB particle formation a bit. In patients with hypertriglyceridemia drugs that slow TG synthesis (fibrates or fibric acids, high dose niacin, or high dose N-3 FA) can reduce apoB-particle formation. Drugs that enhance VLDL catabolism via effects on other surface apolipoproteins and lipases (almost all of the currently available drugs) can also lower apoB.

What current drugs do to apoB or LDL-P

Statin monotherapy: ~ 20-40% lowering (far less efficacious than they are on LDL-C)
Ezetimibe (Zetia) monotherapy: ~ 15-20% lowering
Colesevelam (Welchol) monotherapy: ~ 10-12% lowering
Extended release niacin (Niaspan) monotherapy: ~ 20% lowering. All must understand that niacin is an apoB lowering drug not an HDL particle raising drug.
Slow release niacin is a bit less potent and adds potential liver toxicity at dose > 1500 mg
Fenofibric acid monotherapy: ~ 15%
4000 mg omega-3 FA monotherapy: 2-4%
Raloxifene monotherapy: ~ 12-15% lowering
Sitostanol (Benecol): ~ 5% lowering

Statin/Niaspan or Statin/ezetimibe (depending on statin and dose: 50-60%)
Statin/colesevelam: with potent statin: ~40-45% with glycemic benefit if needed
Statin plus fenofibric acid: ~5% additional apoB but no additional LDL-P lowering
Statin/high dose OM 3 FA: ~ 5-7% apoB with no additional LDL-P lowering

Statin/ezetimibe/high dose Niaspan would be a potent triple therapy for tough cases
Maximal apoB therapy: Statin/ezetimibe/colesevelam/Sitostanol

Most potent apoB therapy for use in statin intolerant patients: Ezetimibe/fenofibrate + colesevelam if needed

What do the drugs do to total HDL-P (remember HDL-C is not an NCEP goal of therapy and neither is HDL-P in any guideline: however emerging evidence does support (after lowering LDL-P) raising HDL-P to reduce CVD events). Also remember what a drug does to HDL-C often has no correlation what it does to HDL-P and a drug that raises apoA-I may not raise total HDL-P

Statin monotherapy: 5-7% increase (with simvastatin, and rosuvastatin and pitavastatin the most potent)
Ezetimibe (Zetia) monotherapy: ~ no help
Colesevelam (Welchol) monotherapy: ~ 5% increase
Extended release niacin (Niaspan) monotherapy: no effect even though it raises apoA-I
Fenofibric acid or gemfibrozil monotherapy: ~ 10% increase
4000 mg omega-3 FA monotherapy: no effect

Statin/Niaspan or Statin/ezetimibe: no effect on HDL-P beyond statin
Statin/colesevelam: with potent statin: ~2-5% increase beyond statin
Statin plus fenofibric acid: ~ 10% beyond statin for a total of15-20% increase with combo
Statin/high dose OM 3 FA: no additional effect

The clear winner in raising total HDL-P is statin plus fenofibric acid combo

Since in the vast majority of at-risk patients, who have TG < 500 mg/dL, high LDL-P (because of its long half-life) is the primary apoB-containing lipoprotein in plasma and after lifestyle we should all be starting as initial therapy (if tolerated) LDL receptor “upregulators” -- statin monotherapy (dosed to get to goal):

When starting a statin there are two options:

1) as first line monotherapy in your patients do not be shy; predict how many LDL receptors you have to upregulate and how much apoB/LDL-P (non HDL-C) lowering will be required to get to goal and then start with the dose of statin that has a chance of achieving that. The sooner apoB is eliminated the better the CV health provided. Thus if you plan to go the statin monotherapy route, most will have to use much larger doses of statins than in the past. Low dose statin monotherapy is for those who have other issues at play (statin intolerance, muscle issues, etc.) or only moderately elevated LDL-P. Use caution with simvastatin at doses > 20-40 mg in a polypharmacy patient. There is little doubt Livalo (pitavastatin) has the cleanest pharmacokinetic and pharmacodynamic profile of all statins.

2) Start with smaller statin dose which can minimize statin side effects) and add to it ezetimibe, extended release niacin or colesevelam. Such combination therapy lowers apoB (LDL-P) as well or better than high dose statin.

The reason statins lose efficacy on LDL parameters as they are titrated (large effect with lower dose and rule of 6s after that) is that statins both increase PCSK9 activity which catabolizes the

upregulated LDLr and/or upregulate hepatic and jejunal Niemann Pick C1L1 (NPC1L1) causing increased intestinal absorption of cholesterol and back flux of cholesterol from bile to hepatocyte: in turn there will be less than expected hepatic LDLr upregulation with statin monotherapy titration.

My preference for very high, high or even moderately high risk patients is to use your desired statin dose plus ezetimibe or niacin or colesevelam or Benecol (never a plant sterol unless you monitor sitosterol levels). For those with extreme hyperbetalipoproteinemia (LDL-P > 2000 nmol/L, apoB > 120-130 mg/dL), I'd use potent statin (Crestor 20 titrated to 40 mg) plus LDLr upregulator add-on therapy. There is a combination statin/ezetimibe product (Vytorin) or statin/Niaspan product (Simcor) available but caution with the simvastatin drug-drug interactions (with simvastatin doses ≥ 40 mg) and of course 80 mg is no longer allowed in those who have not been on it for > 1 year. So for the nightmare LDL-P patients I'd prefer Crestor 20-40/Zetia or Crestor/Niaspan. An intriguing emerging combination is to use pitavastatin (Livalo) as the statin choice as it has the cleanest pharmacotherapy of all statins, raises apoA-I more than other statins and does not seem to aggravate glycemic parameters or be associated with T2DM onset.

On the return visit for those receiving statin (or other) monotherapy, if non-HDL-C (or apoB or LDL-P) remains high, combination therapy as well as more aggressive lifestyle is indicated. Here is a simple, easily understood algorithm, for those using the lipid profile of getting non-HDL-C to goal if statin monotherapy has not done so or for those doing NMRs or apoB, how to achieve lipoprotein goals. You will save a lot more lives and reduce CHD morbidity by using lipoprotein measurements

Non-HDL-C = TC minus HDL-C or VLDL-C plus LDL-C
VLDL-C is determined by dividing TG by 5
But always remember that elevated non-HDL-C is it is simply an LDL-P surrogate in most cases.

Thus the higher the TG, the higher will be the VLDL-C. Anyone with a TG > 150 has high VLDL-C (> 30 mg/dL) and unless the LDL-C is very low, a high non-HDL-C. Thus, non-HDL-C translates TG into cholesterol. As superior to LDL-C as non-HDL-C is, it still misses upwards of 30% of those with high LDL-P (that is called discordance). So please when non-HDL-C gets too goal, then do an LDL-P to be sure all atherogenic particles are at goal. Many including the AACC are realizing that a perfect TG is < 70 mg/dL and thus a normal VLDL-C is not 150/5 or 30 mg/dL but 70 to100 divided by 5 or 15-20 mg/dL. I recommend in high and very high risk patients to use 15 instead of 30 when determining the non-HDL-C goal

So if on a statin, non-HDL-C is still elevated we need to know is the non-HDL-C increase being driven by 1) LDL-C, 2 VLDL-C (TG), 3 predominantly low HDL-C (unusual) or 4) a combination of all. In reality what we need to know is what is the LDL-P (apoB)? If those two are fine, dismiss the non-HDL-C. If you cannot get particle measurements you have to use non-HDL-C, never LDL-C by itself (non-HDL-C includes LDL-C).

Scenario 1) High LDL-C and non-HDL-C with normal TG (< 100 mg/dL) and HDL-C

Advanced testing: High apoB Normal apoA-I
NMR data: Elevated Total LDL-P: VLDL-P and HDL-P normal

Therapy: add ezetimibe (Zetia) or colesevelam (Welchol) or Niaspan or Benecol or ultimately any combination or all to the statin: Use clinical judgment as to whether Vytorin (a combo product which will reduce co-pays) or will likely get one to goal or if the ultimate apoB therapy rosuvastatin/ezetimibe (Crestor/Zetia) will be required. If insulin resistance is at play despite the normal TG, Livalo has the least propensity to cause diabetes onset or aggravate glycemic issues. Many believe it is also the statin with the least muscle side effects and for sure the one with the least drug-drug interactions. Keep in mind Niaspan must be used at 1500-2000 mg.

If statin intolerant: consider ezetimibe (Zetia) plus colesevelam (Welchol) plus a plant stanol (Benecol) plus aggressive low saturated fat diet. Recent data showed ezetimibe/fenofibrate was also efficacious in patients without the metabolic syndrome.

Scenario 2) High VLDL-C (TG elevated), LDL-C normal, with HDL-C usually low (but may be normal), and non-HDL-C high

Note: If you believe a TG of 150 is normal then a normal VLDL-C is < 30. If you believe as do many lipidologists that a TG of 70 mg/dL is desirable then a VLDL-C of 15 is normal. Be aware that a recent AHA statement on TG declared an optimal TG to be less than 100 mg/dL. What value you assign to VLDL-C is crucial because non-HDL-C goals are obtained by adding the normal (desired) VLDL-C to the appropriate LDL-C goal: i.e., 70 plus 30 or 100 mg/dL or 70 plus 10-15 or 80-85 mg/dL for the very high risk patient or 100 plus 30 or 130 mg/dL or 100 +15 or 115 mg/dL for the high risk patient

Note in such patients, glucose intolerance and insulin resistance is often present: hypertension and hyperuricemia as well and that can influence add-on therapy. Monitor closely with niacin use.

Advanced testing: High apoB
NMR testing: Elevated Total and small LDL-P: Increased VLDL-P and decreased Total HDL-P Reduced large HDL-P. LP-IR score elevated in drug naïve patients

Therapy: Add ezetimibe (Zetia) or add Niaspan (could switch to Vytorin or Simcor). Keep in mind Niaspan must be used at 1500-2000 mg. Adding colesevelam could help and improve glycemic issues. Benecol always helps a bit. If the duo therapies do not achieve goals, triple or quadruple therapies are needed. As long as LDP is dropping show no concern if colesevelam causes a mild increase in TG.

Fenofibrate/ezetimibe is an approved FDA therapy that can be quite effective in reducing non-HDL-C but this should be reserved for statin intolerant patients. Extended-release niacin (Niaspan) added to Zetia can also be used, but 2000 mg are needed for effective TG benefit in most patients. In general, should not be used before a fibrate in T2DM. In severe cases ezetimibe/fenofibrate/Niaspan is used with colesevelam also possible.

Scenario 3) Low HDL-C, TG not very high (<150) LDL-C OK, non-HDL-C may be high but might be normal by NCEP values (so called isolated HDL-C).

Advanced testing: Elevated apoB Decreased apoA-I Abnormal apoB/apoA-I ratio
NMR testing: Elevated Total and usually small LDL-P. Large VLDL-P may be slightly up. Both Total HDL-P and Large HDL-P quite low.

If apoB or LDL-P is normal, this is likely a genetic hypoalphalipoproteinemia likely not associated with significant CHD risk and thus therapy may not be needed: screen for subclinical CHD to be sure.

Therapy: 1) Get LDL-P and apoB to goal: so adding ezetimibe (Zetia) or Niaspan (or using Vytorin or Simcor) is a start. However those two add-ons do not affect HDL-P, so the following is also a strategy to increase total HDL-P:

> I'd prefer Livalo or pitavastatin at 4 mg as it is the best apoA-I raising statin) to which I would add fenofibric acid, which is the only other lipid drug aside from a statin that can raise total HDL-P. If ezetimibe or Niaspan is needed to get LDL-P/apoB to goal so be it. Neither of those would help HDL-P.

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Scenario 4) High LDL-C and VLDL-C (combined hyperlipidemia), High non-HDL-C, HDL-C often low:

Advanced testing: Elevated apoB & decreased apoA-I
NMR: Elevated Total LDL-P (large and/or small) Elevated VLDL-P (especially large), Decreased Total and large HDL-P

Therapy: depending on how elevated apoB or non-HDL-C is add to the statin ezetimibe (Crestor/Zetia or Vytorin) or Niaspan titrated to 2000 mg (cannot use Simcor if simvastatin dose is 80 mg). Can consider colesevelam if glycemic issues are a problem or use any combo of the above mentioned meds (statin/ezetimibe/high dose Niaspan/colesevelam).

If an HDL-P increase is needed fenofibrate or fenofibric acid (Trilipix) can be used. For raising total HDL-P, Livalo is likely the best statin. Fenofibrate or fenofibric acid as well as very high dose Omega-3 FA can address TG issues and VLDL-P issues (apoB) but not the LDL-P. Feno products significantly raise HDL-P, high dose omega-3 FAs do not.

STATIN Intolerance Options:

Scenario 1) Ezetimibe (Zetia) plus fenofibrate or fenofibric acid (Trilipix) plus plant stanol (Benecol)

Scenario 2) Fenofibrate (TriCor, Lipofen, etc.) or fenofibric acid (Trilipix) plus ezetimibe (Zetia) plus Niaspan plus N-3 FA Whatever it takes.

Scenario 3) Fenofibrate (TriCor, Lipofen, etc.) or fenofibric acid (Trilipix), plus extended-release niacin (Niaspan) plus ezetimibe (Zetia) plus N-3 FA plus Stanol plus Welchol (colesevelam)

Forn the very high TG patient: > 500 mg/dL (lifestyle and glycemic control crucial): Stop all carbs.

Start 4000mg Omega-3 FA (Lovaza) or fenofibrate or fenofibric acid or both

If TG still not < 500 mg/dL, add Niaspan titrated to 2000 mg. Can go to 6000 mg Omega-3 FA

If still not < 500 mg/dL add Crestor titrated to 40 mg or Lipitor to 80 mg

Orlistat (major GI limitations).

Off label: Actos (too many downsides to this for me), Victoza, testosterone