Ezetimibe and LDL Particles

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There is emerging data on ezetimibe (Zetia) and LDL particle size, but because Zetia does not affect triglyceride synthesis, one would not expect it to have much effect. There is a publication looking at a few patients where Zetia did nothing to LDL size although it lowered the more important LDL particle concentration (LDL-P). **Cardiovascular Drugs and Therapy 18 327–328 2004**

Hepatic production of triglycerides (TG) is what creates small LDL and HDL. The only drugs that consistently effect (increase) particle size are those that inhibit the synthesis of TG: fibrates, niacin, omega-3 FA, TZDs. But keep in mind that particle size is not an independent risk factor for CHD and that altering particle size has no statistically significant relationship with event reduction. Of course normalizing LDL-C or apoB or LDL-P (LDL particle concentration or apoB) has a strong relationship with CHD event reduction.

The major MOA of statins and ezetimibe is to deplete the liver of cholesterol (statins by synthesis inhibition and ezetimibe by Niemann Pick C1 Like 1 (NPC1L1) blockade. NPC1L1 is expressed in jejuna enterocytes and at the hepatobiliary interface and thus reduces enterocyte absorption of sterols as well as hepatic reabsorption of biliary sterols): This dual blockade of hepatic cholesterol sources activates sterol regulatory element binding proteins (SREBPs) which in turn which causes an upregulation of hepatic LDL receptors (LDLr). These receptors attach to apoB on the surface of LDLs (as well as VLDLs and IDLs) and internalize the LDL particles into the liver (in effect removing them from plasma). However, LDL receptors more easily recognize and attach to the apoB conformation on large rather than small LDL particles.

That concept supports the rationale that in patients with small LDL particles combination therapy with statins, statins/ezetimibe and drugs that shift LDL size such as fibrates or niacin makes great sense. The fibrates and niacin would shift LDL size to a larger phenotype and those particles would be more easily recognized and removed by statin/ezetimibe induced upregulation of LDL receptors. Zetia is FDA approved to combine with fenofibrate (never gemfibrozil): there is no known interaction between fenofibrate and simvastatin so I would not envision much risk combining Vytorin (or any other statin/ezetimibe combination) and fenofibrate. There is little in the package insert on combining ezetimibe and niacin, but they should also work well together. There is a nice study showing significant efficacy when Niaspan is added to Vytorin. (J Am Coll Cardiol 2008;51:1564–72)