Fibrates & N3 FA and LDL Size and LDL-C

Thomas Dayspring MD, FACP

VLDLs are TG-rich lipoproteins that after secretion by the liver undergo lipolysis (hydrolysis of TG into fatty acids). The lipolytic process, because it is removing lipids shrinks the particle. Thus a VLDL undergoing lipolysis becomes a transient IDL some of which becomes LDLs. The ones that do not become IDLs and LDLs are cleared by the liver LDL receptors or LDL receptor related protein.

Insulin resistant persons, because of a number of abnormalities with lipolysis (decreased apoA-V, increased apoC-III, defective apoE, lipoprotein lipase deficiency) have delayed lipolysis of their TG-rich lipoproteins (VLDL and IDL). This explains the fasting and postprandial hypertriglyceridemia in these folks.

Fibrates and N-3 FA speed the lipolytic process through numerous actions (see below): Thus fibrates and N-3 FA cause a more rapid lipolysis of VLDLs into LDLs. VLDL-C goes down and LDL-C goes up.

Also when TG-rich lipoproteins are present, they swap (using cholesteryl ester transfer protein or CETP) their TG for cholesteryl ester (CE) inside particles that do not have many TG (LDL and HDL). This makes the LDL and HDL particles cholesterol-poor and TG-rich. When such particles pass through the liver and are exposed to hepatic lipase they loose the TG creating small LDL particles. Because fibrates and N-3 FA decrease the synthesis of TG, and thus the amount of TG within VLDLs, there will be less CETP-mediated swapping of LDL and HDL cholesteryl ester for TG. This will tend to prevent the formation of small LDL and HDL (in effect increasing HDL-C and LDL-C).

So, these drugs increase LDL-C by rapidly changing VLDLs into LDLs and by increasing the size of LDL particles. Both lower apoB. In the COMBOS trial it was necessary for N3-FA to reduce the TG to < 150 before LDL size was impacted.

How do the drugs decrease TG?

Fibrates

- Increase hepatic beta-oxidation of FA: less substrate to make TG
- Increased beta-oxidation of FA
- Inhibit DGAT, an enzyme which attaches FA to diacyglycerol forming TG
- Increase lipoprotein lipase production (the major triglyceridase in plasma)
- Increase production of apoA-V (enhances lipolysis)
- Decreases production of apoC-III (increases lipolysis)
- Decreases CETP activity

N-3 FA

- Increase hepatic beta-oxidation of FA: less substrate to make TG
- Inhibit fatty acid synthesis
- Probably Inhibit DGAT, an enzyme which attaches FA to glycerol
- Increase lipoprotein lipase activity (the major triglyceridase in plasma)
- The resultant drop in TF decreases CETP activity
- Increase endoplasmic and post endoplasmic presecretory proteolysis of apoB (a protein used in manufacturing VLDLs)