N-3 Fatty Acids Non-HDL-Cand LDL-C

Thomas Dayspring MD, FACP

Omega or N-3 Fatty Acids (FA) significantly reduce TG synthesis and significantly deplete the TG content of VLDL particles indicated by significantly reduced VLDL-C. FA are the substrate for TG synthesis. N3-FA reduce TG synthesis by reducing hepatic FA concentrations (decreased FA synthesis and increased beta-oxidation of FA) and they inhibit diacylglycerol acyl transferase 2 (DGAT2) the enzyme that esterifies (adds FA) to diacylglycerols creating triacylglycerol or TG.

Thus the VLDLs in patients taking high dose N3-FA will carry less TG (the VLDL will be smaller). The VLDLs with less TG can be readily hydrolyzed by lipoprotein lipase whose activity is also increased by N3-FA. The hydrolysis of the VLDL-TG will shrink the VLDL - large chunks of surface phospholipids break off and attach to phospholipid transfer protein. Smaller VLDLs, carrying less TG, suppress cholesteryl ester transfer protein (CETP) activity: thus as VLDL-TG drops there is less CETP mediated swapping of TG between VLDLs and both LDLs and HDLs: therefore the LDLs and HDLs retain their cholesterol instead of transferring it to VLDL. This prevents LDL-C and HDL-C from dropping and VLDL-C from rising – in other words with less CETP activity the LDLs and HDLs keep their cholesterol content.

As the VLDLs attach to lipoprotein lipase and undergo lipolysis they, by loosing surface phospholipids and core TG, become smaller VLDLs or become IDLs: Because of their significant surface apolipoprotein E and their single molecule of apoB many of the VLDLs and IDLs are cleared (endocytosed) by hepatocyte LDL receptors -- this is part of the indirect reverse cholesterol transport system and it helps to reduce apoB and drastically reduce VLDL-C. The smaller VLDL and resultant IDL assume a size and a shape more recognizable by hepatic LDL receptors as well as the LDL receptor related protein. Their high surface concentration of apoE as well as their single apoB serves as ligands for those hepatic receptors.

However **some** of the small VLDLs and IDLs are further hydrolyzed by hepatic lipase (a liver located lipase which hydrolyzes both core TG and surface phospholipids). This lipolytic process converts the small VLDLs and IDLs to smaller apoB particles, namely large LDLs. These LDLs join the already existing LDLs -- raising LDL-C. However because the larger LDL is more amenable to LDL receptor recognition and removal, the LDL half-life goes down: keep in mind the LDLs before the N3-FA administration were small (because TG were high) and small LDLs have a half-life of 5-6 days and larger ones 2-3 days.

So N3-FA therapy increases conversion of some VLDLs to larger LDLs increasing LDL-C. However since there is increased hepatic clearance of VLDLs and large LDLs and the remaining LDLs are much larger than they were: so apoB goes down and LDL-C goes up. Since particle number (apoB or LDL-P) is the major risk factor for atherosclerosis the slight rise in LDL-C does not impart CV risk.

Using my dump truck (lipoprotein) analogy: N3-FA makes the liver produce VLDL dump trucks that are depleted in their TG load and thus much smaller than previous dump trucks produced when TG were high. After they deliver their TG to muscles and/or adipocytes, the VLDL dump trucks further reduce in size return to the liver for removal (VLDL-C goes down) instead of hanging around longer in the plasma. Some of those small VLDL dump trucks become IDL dump trucks and big LDL dump: many of those IDL and LDL trucks are also cleared by the liver. Overall the number of VLDL and LDL dump trucks goes down, but the remaining LDL dump trucks are larger than the smaller ones that used to be there when TG were high. Thus even though there are less LDL dump trucks than before (apoB or dump truck number is reduced), those dump trucks are much larger and thus they are carrying more cholesterol than did the more numerous smaller dump trucks.

Back to science: Because of their potent TG reducing capabilities, N3-FA also reduce VLDL-C, HDL-C but they can raise LDL-C.

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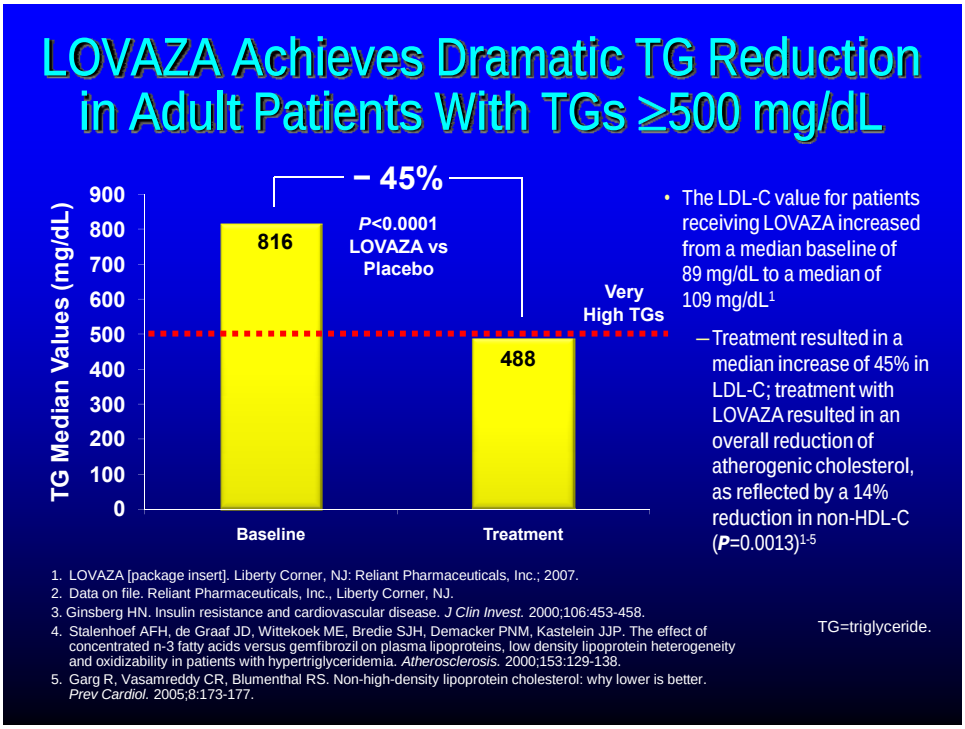
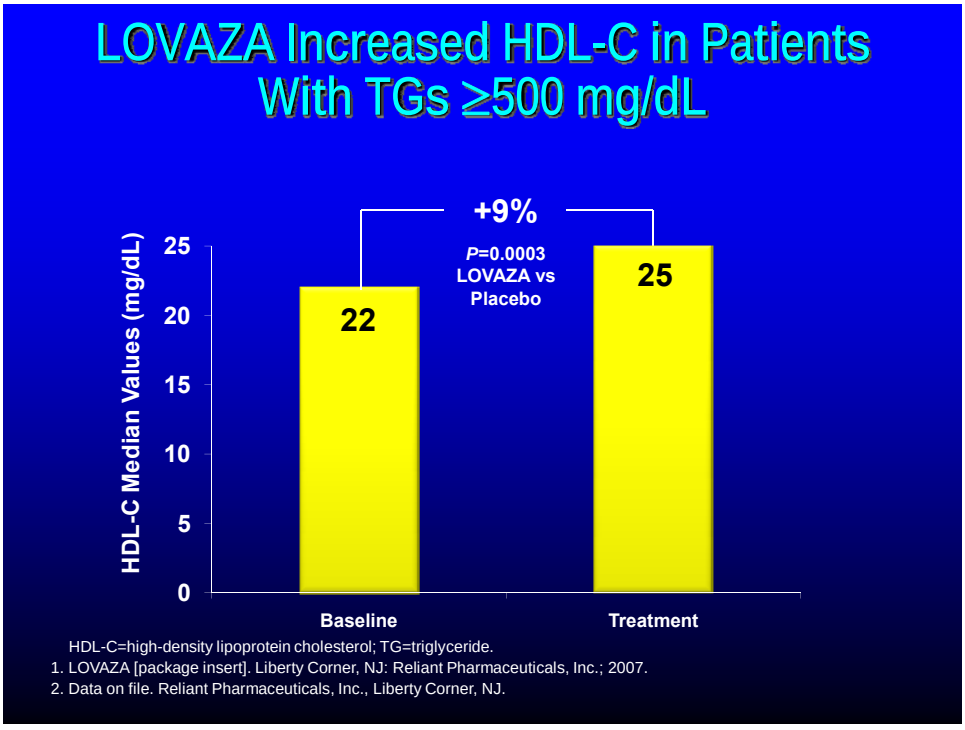
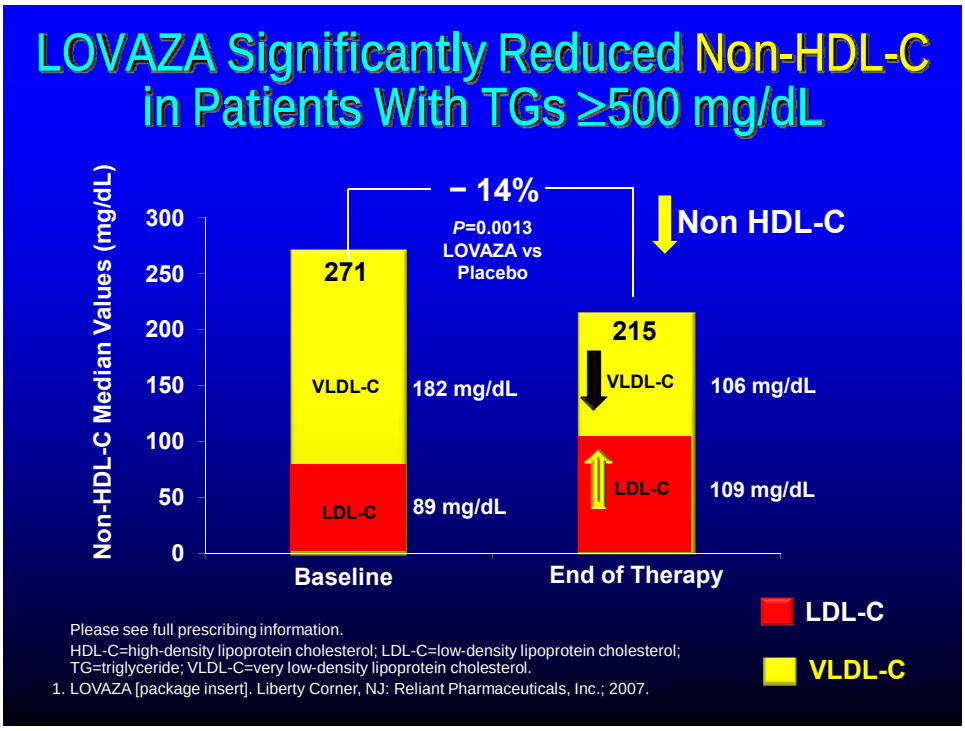
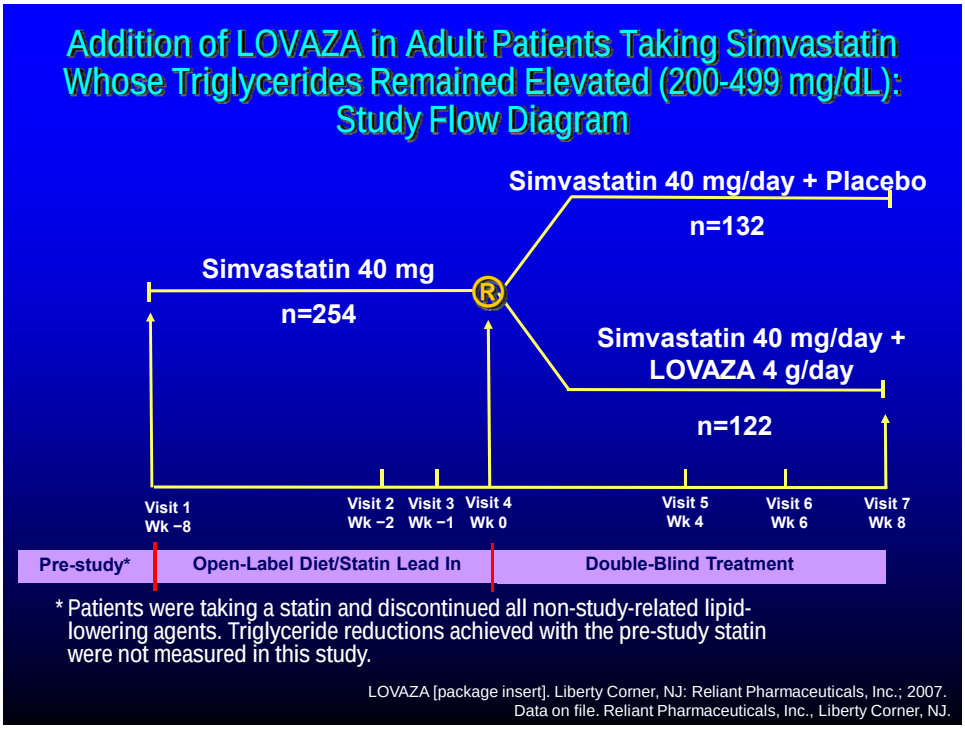
Non-HDL-C (the apoB surrogate) = VLDL-C plus LDL-C. Since the VLDL-C reduction is vastly more dramatic than the LDL-C rise, N3-FA reduces non-HDL-C (apoB). The LDL-C rise has no clinical meaning other than it is an indicator of increasing LDL size.

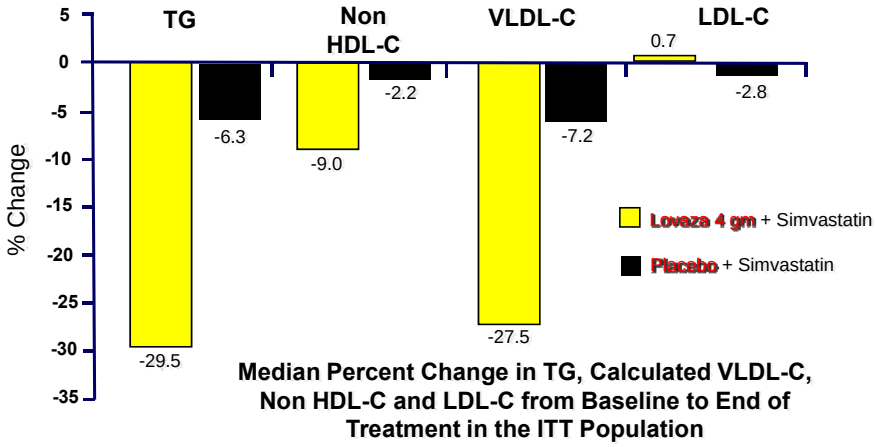





LOVAZA Significantly Reduced Non-HDL-C in Patients With TGs ≥500 mg/dL
Non-HDL-C Median Values (mg/dL)
300
250
200
150
100
50
0
− 14%
P=0.0013
LOVAZA vs Placebo
Non HDL-C
271
VLDL-C
182 mg/dL
LDL-C
89 mg/dL
215
VLDL-C
106 mg/dL
LDL-C
109 mg/dL
Baseline
End of Therapy
LDL-C
VLDL-C
Please see full prescribing information.
HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride; VLDL-C=very low-density lipoprotein cholesterol.
1. LOVAZA [package insert]. Liberty Corner, NJ: Reliant Pharmaceuticals, Inc.; 2007.


Addition of LOVAZA in Adult Patients Taking Simvastatin Whose Triglycerides Remained Elevated (200-499 mg/dL): Study Flow Diagram
Simvastatin 40 mg/day + Placebo
n=132
Simvastatin 40 mg
n=254
R
Simvastatin 40 mg/day + LOVAZA 4 g/day
n=122
Visit 1 Wk −8
Visit 2 Wk −2
Visit 3 Wk −1
Visit 4 Wk 0
Visit 5 Wk 4
Visit 6 Wk 6
Visit 7 Wk 8
Pre-study*
Open-Label Diet/Statin Lead In
Double-Blind Treatment
* Patients were taking a statin and discontinued all non-study-related lipid-lowering agents. Triglyceride reductions achieved with the pre-study statin were not measured in this study.
LOVAZA [package insert]. Liberty Corner, NJ: Reliant Pharmaceuticals, Inc.; 2007.
Data on file. Reliant Pharmaceuticals, Inc., Liberty Corner, NJ.

COMBination of Prescription Omega-3s with Simvastatin: (COMBOS)

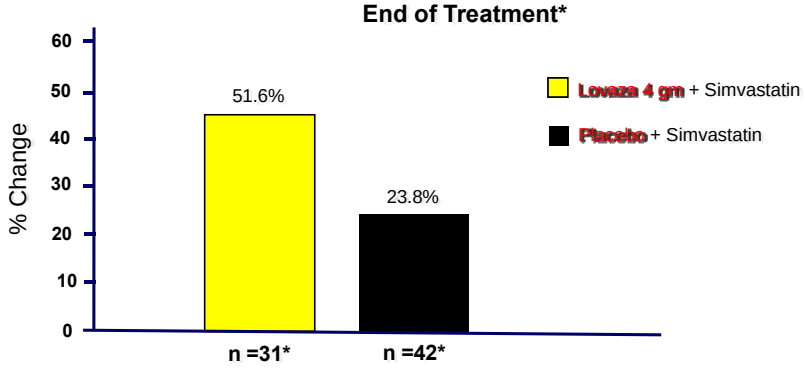


Median Percent Change in TG, Calculated VLDL-C, Non HDL-C and LDL-C from Baseline to End of Treatment in the ITT Population

Davidson MH et al. Clin Ther 2007;29:1354-1367

COMBination of Prescription Omega-3s with Simvastatin: (COMBOS)

Percentage of Patients Achieving Non HDL-C Goal at End of Treatment*



*Not at Non HDL-C goal at baseline

Davidson MH et al. Clin Ther 2007;29:1354-1367

COMBination of Prescription Omega-3s with Simvastatin: (COMBOS)