

Statins and Triglycerides

Since statins have very different abilities to lower cholesterol it should not surprise anyone that the same is true with respect to TG. If someone asked you name the two most potent statins at lowering LDL-C one would shout Crestor (rosuvastatin) 40 mg and Lipitor (atorvastatin) 80 mg (no difference between the two). The data supporting this is the STELLAR trial. Well what a shock, those same two statins at those doses are the most potent TG-lowering statins. (Am J Cardiol 2003;93:152–160). The mechanism of action is the same as how they lower LDL-C.

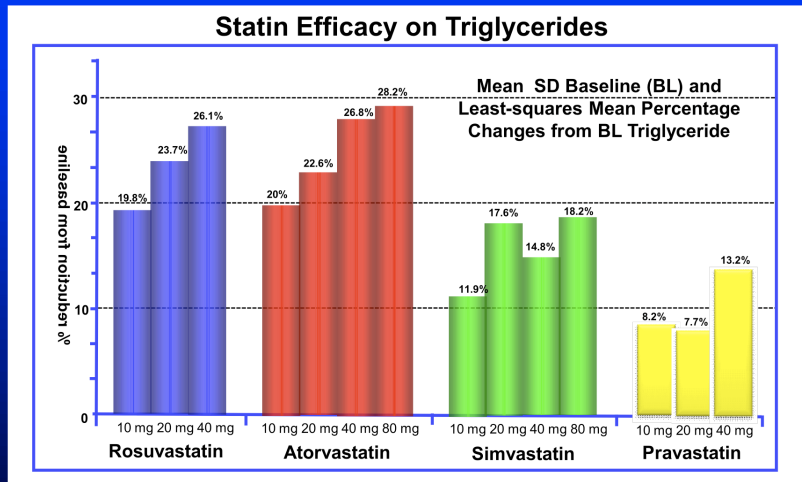
Depletion of hepatic cholesterol pools by statin-induced inhibition of HMGCoA reductase, leads to both decreased production of apoB-containing VLDL particles and especially to upregulation of LDL receptors (LDLr) which bind to the apoB on LDL particles and then internalizes the LDL particles into the liver for catabolism: clinically both of these actions leads to reductions in apoB, non-HDL-C and LDL-C. Well guess what: chylomicrons and VLDLs are the major TG-trafficking lipoproteins and on their surface is not only apoB 100 (VLDLs) but multiple copies of apoE (chylomicrons and VLDLs). ApoE is also a ligand for the LDLr. Chylomicrons, because they are so much bigger, have more copies of apoE than due VLDLs and will be preferentially cleared over VLDLs. Therefore, the statins that inhibit cholesterol synthesis the most (rosuvastatin binds more tightly to HMGCoA reductase than other statins), will upregulate the most LDL receptors and enhance maximal clearance of the TG-rich VLDLs and chylomicrons. This will clearly reduce TG levels, but most importantly lead to additional apoB reduction beyond clearance of the LDLs. This concept is so critical because it explains when statins lower TG, they are really removing apoB particles that are present in excess quantities in those with elevated TG (these particles are chylomicron remnants, VLDLs, VLDL remnants, TG-rich large LDLs and small LDLs).

One other factor affects how much TG lowering will occur with statins and that is the baseline level of the TG. Statins are much better at reducing TG when levels are > 200 mg/dL than when the levels are lower. Patients with TG > 200 mg/dL are usually insulin resistant and for a multitude of reasons have delayed lipolysis of TG-rich lipoproteins (VLDLs). Under such circumstances the VLDL half life goes from 2-6 hours (normal) to 12-16 hours (delayed). This results in lots of TG-rich lipoproteins which can be "grabbed" by the statin upregulated LDLr. People with TG < 200 mg/dL simply have more rapid VLDL clearance and much lower VLDL-P levels and the statins have much less of an impact on reducing VLDL-P and TG.

Statins and Triglycerides

Since statins lower TG by endocytosing TG-rich apoB particles, the TG themselves are simply re-compartmentalized by going from plasma into the liver. Although some of these TG may be de-esterified to glycerol and FA which can be oxidized, the rest will just be stored in the liver or again secreted in newly formed VLDLs.

Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR)



6-week, parallel-group, open-label, randomized, multicenter trial of 2431 patients (men and women)

Jones PH et al. *Am J Cardiol* 2003;93:152-160

There are other ways to lower TG. One is to reduce TG synthesis by reducing hepatic FA levels by reducing FA synthesis (lipogenesis) or enhancing FA mitochondrial oxidation in the liver. Since FA are the key substrate for TG synthesis, TG formation will be reduced. Diacylglycerol acyl transferase (DGAT) is a key enzyme in TG production (attaches the final acyl group to diacylglycerol thereby forming triacylglycerol). Inhibiting DGAT slows TG production. All of these steps lower TG production: VLDL production is reduced and the VLDLs that are made will carry less TG. One can also enhance TG hydrolysis in plasma (via lipases). Diet, fibrates, high dose niacin and high dose N-3 FA do all of the aforementioned. --- blocking FA absorption with orlistat (Xenical) would also reduce FA levels thereby reducing substrate for TG production.

In STELLAR trial although there was no difference in TG lowering between high dose rosuvastatin and atorvastatin, the rosuvastatin was superior in improving all other lipid and lipoprotein fractions. Never forget that when treating patients with high TG, the NCEP ATP-III goal is not the TG level per se, but rather reduction of non-HDL-C which of course is the surrogate of apoB particles associated with TG

Statins and Triglycerides

elevations (chylomicrons and VLDL remnants, small LDLs). The best lipid surrogate of apoB is non-HDL-C. ApoB is the goal of therapy of the ADA/ACC Consensus Statement on Lipoprotein management in Patients with Cardiometabolic risk - i.e. hypertriglyceridemia). Rosuvastatin is the superior statin monotherapy on that non-HDL-C, apoB and LDL-P, as it clears more LDL particles than does the atorvastatin. Clinicians must come to realize they are not really treating TG per se, but rather the apoB particles present in patients with elevated TG. ApoB (non-HDL-C) is the NCEP goal of therapy, not TG. Unfortunately there is no clear cut relationship between specific TG levels and apoB (LDL-P). Since high dose rosuvastatin lowers apoB more than does high dose atorvastatin, I prefer to use rosuvastatin as the statin of choice in patients with high TG. If apoB (LDL-P and VLDL-P) goal is not reached adding a fibrate, niacin or omega-3 makes sense as statin add-ons in persons with high TG.

Lastly in the ENHANCE trial and other statin/ezetimibe trials there was significantly more TG-lowering when ezetimibe (Zetia) was added to a statin than statin monotherapy. The reason is simple: ezetimibe by further depleting hepatic cholesterol pools upregulates additional LDLr beyond those induced by the statins. Additional apoB-containing TG-rich lipoproteins will be cleared from plasma. Indeed in clinical practice many patients with high levels of TG induced apoB particles will require statin/ezetimibe plus fibrate, niacin or high dose omega-3 (triple) therapy.