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International Journal of Chemistry and Pharmaceutical Sciences

2013, Vol.1 (2): 180-186

ISSN 2321-3132



Review Article



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## A Review on Statin Co-Administration with Ezetimibe or Niacin for the Treatment of Hypercholesterolemia, and other Diseases

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### ABSTRACT

Hypercholesterolemia disease treatment with HMG-CoA reductase inhibitors has been very successful. There is increasing interest in adding other lipid lowering therapy, primarily as additional therapy onto HMG-CoA reductase therapy. This paper will examine two of the more popular secondary agents, ezetimibe and niacin, and describe for usefulness in further reducing cardiovascular events.

**Key words:** Statins, Ezetimibe, niacin, Hypercholesterolemia, coronary heart disease

### Introduction

Cholesterol is a fat (lipid) which is produced by the liver and is crucial for normal body functioning. Cholesterol exists in the outer layer of every cell in our body and has many functions. It is a waxy steroid and is transported in the blood plasma of all animals. It is the main sterol synthesized by animals - small amounts are also synthesized in plants and fungi. In the human body there are two major sources of cholesterol: first, the gastrointestinal tract where daily cholesterol is derived from the diet, bile input and desquamated cells; second, the liver which is the major source of cholesterol synthesis; in the human body. Approximately 50% of the cholesterol pool is absorbed and recirculated through the intestine, while the remainder is excreted through the feces. A recent and more effective therapeutic strategy, is to treat both sources of cholesterol simultaneously with a complementary mechanism of action, by co-administering ezetimibe, a novel agent inhibiting cholesterol absorption, together with a statin, which

inhibits cholesterol production in the liver. This results in dual inhibition of both sources of cholesterol provides significantly greater LDL-C reduction and subsequent goal attainment.

### 1. Exogenous pathway

Route of uptake of dietary lipids Chylomicrons (CM) are complexes of triglycerides (TG), cholesteryl esters (CE), and apoproteins. After the removal of triglycerides they become chylomicron remnants. Chylomicrons are degraded by lipoprotein lipase on endothelial cells of adipose tissue and muscle. After removal of TG for storage, the CM remnants are transported to the liver. This results in dietary TG stored in adipose tissue and muscles.

### 2. Endogenous pathway

Route for distribution of cholesteryl esters (CE) from liver to target cells VLDL is secreted by the liver into plasma and transported to adipose tissue and muscles, where lipoprotein lipase extracts most triglycerides. The remnant IDL is either taken up by the liver or circulated until the remaining triglycerides are removed forming LDL particles, rich in cholesterol. LDL is cleared from plasma through LDL receptor-mediated endocytosis. This results in transfer of TG from liver to target cells via VLDL, as well as, transfer of CE from liver to target cells via LDL.

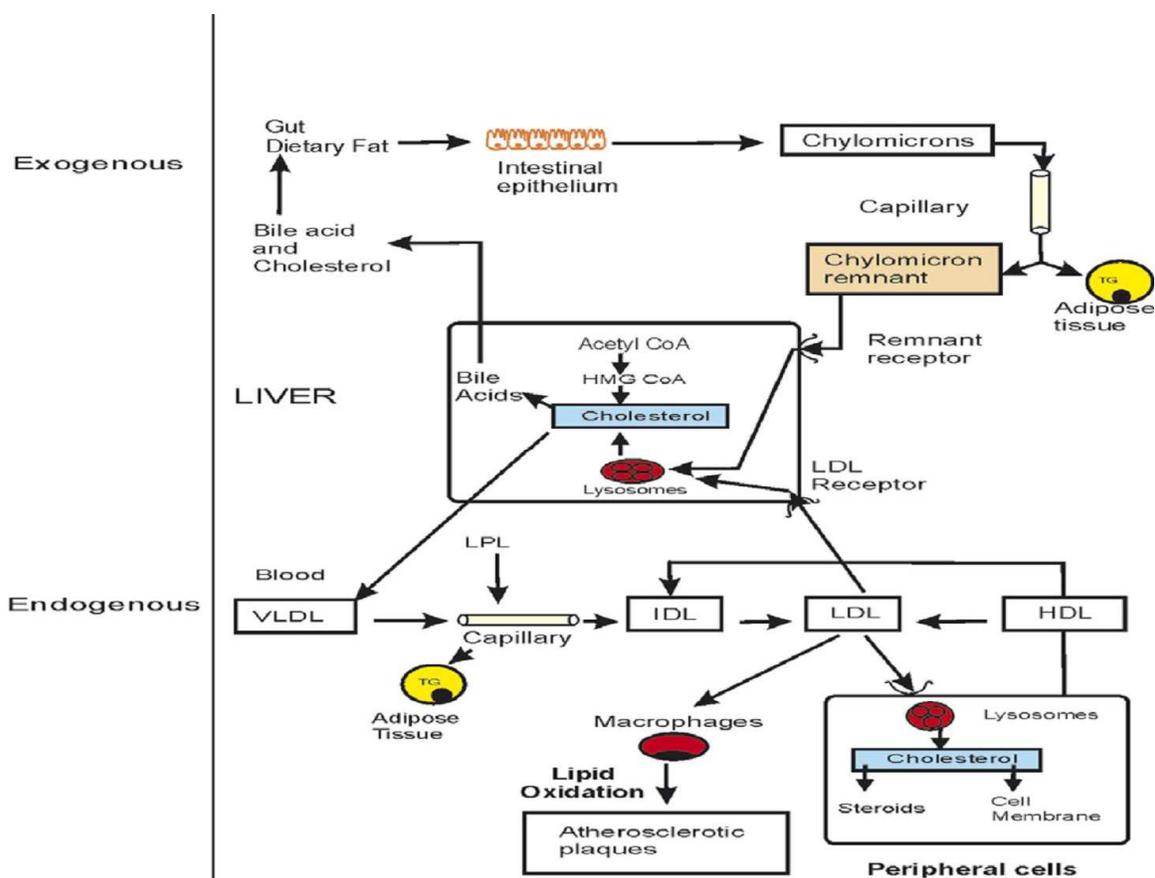


Fig.1 Endogenous and exogenous transport of lipids

### Cholesterol excretion by enterohepatic circulation:

Bile salts are synthesized from cholesterol in the liver, released into the intestine, and recycled. A small amount of bile acid is excreted. This results in conversion of liver cholesterol to bile salts for excretion.

### Types of Lipoproteins<sup>2</sup>

Cholesterol is carried in the blood by molecules called lipoproteins. A lipoprotein is any complex or compound containing both lipid (fat) and protein. The three main types are:

**LDL (low density lipoprotein)**

People often refer to it as bad cholesterol. LDL carries cholesterol from the liver to cells. If too much is carried, too much for the cells to use, there can be a harmful buildup of LDL. This lipoprotein can increase the risk of arterial disease if levels rise too high. Most human blood contains approximately 70% LDL - this may vary, depending on the person.

**HDL (high density lipoprotein)**

People often refer to it as good cholesterol. Experts say HDL prevents arterial disease. HDL does the opposite of LDL - HDL takes the cholesterol away from the cells and back to the liver. In the liver it is either broken down or expelled from the body as waste.

**Triglycerides**

These are the chemical forms in which most fat exists in the body, as well as in food. They are present in blood plasma. Triglycerides, in association with cholesterol, form the plasma lipids (blood fat). Triglycerides in plasma originate either from fats in our food, or are made in the body from other energy sources, such as carbohydrates. Calories we consume but are not used immediately by our tissues are converted into triglycerides and stored in fat cells. When your body needs energy and there is no food as an energy source, triglycerides will be released from fat cells and used as energy - hormones control this process.

According to the National Health and Nutrition Examination Survey and the National Cholesterol Education Program Adult Treatment Panel III, an estimated 100,870,000 American adults have total cholesterol levels  $\geq 200$  mg/dL and are at increased risk of developing coronary heart disease.

**Cholesterol-Controlling Medications<sup>2</sup>**

If your cholesterol levels are still high after doing everything mentioned above, your doctor may prescribe a cholesterol-lowering drug. They may include the following:

**Statins (HMG-CoA reductase inhibitors)**

These block an enzyme in your liver that produces cholesterol. The aim here is to reduce your cholesterol levels to under 4 mmol/liter and under 2 mmol/liter for your LDL. Statins are useful for the treatment and prevention of atherosclerosis. Side effects can include constipation, headaches, abdominal pain, and diarrhea. Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin are examples of statins.

**Aspirin:** This should not be given to patients under 16 years of age.

**Drugs to lower triglyceride levels:** These are fibric acid derivatives and include gemfibrozil, fenofibrate and clofibrate.

**Niacin:** This is a B vitamin that exists in various foods. You can only get very high doses with a doctor's prescription. Niacin brings down both LDL and HDL levels. Side effects might include itching, headaches, hot flashes (UK: flushes), and tingling (mostly very mild if they do occur).

**Anti-hypertensive drugs** - If you have high blood pressure your doctor may prescribe Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin II receptor blockers (ARBs), Diuretics, Beta-blockers, Calcium channel blockers. In some cases cholesterol absorption inhibitors (ezetimibe) and bile-acid sequestrants may be prescribed. They have more side effects and require considerable patient education to achieve compliance (to make sure drugs are taken according to instruction).

**Hmg-Coa Reductase Inhibitors<sup>3</sup>**

The HMG-CoA reductase inhibitors, or "statins" as they are frequently called, have revolutionized the management of cardiovascular disease. Their mechanism of action involves the inhibition of the HMG reductase step in the production of cholesterol in the liver. This leads to a reduction of hepatic cholesterol levels, thus stimulating the Low Density Lipoprotein, or LDL-C, receptor sites on the hepatic cells. The stimulated LDL-C receptors increase their binding of LDL-C in the blood stream, lowering the serum LDL-C levels. The degree of LDL-C lowering differs within the statin class, with the original agents, pravastatin and lovastatin having the least LDL-C lowering, while the newer statins, rosuvastatin and atorvastatin, produce the most potent lowering of LDL-C.

In addition to lowering LDL-C by anywhere from 20% to 63%, the statins also lower total cholesterol and triglycerides by different amounts. All of the statins except atorvastatin also increase High Density Lipoprotein, or HDL-C, also in amounts that vary between the agents. Atorvastatin can also lower HDL-C, an anomaly that is not completely understood.<sup>6</sup> The statin treatment trials show that this class of agents is extremely successful in reducing heart attack and other cardiovascular events in at-risk patients. Clearly, much of this benefit is mediated through the lowering of LDL-C. However, whether the same degree of benefit would be seen with agents from the medication classes other than the statins is unproven and therefore a point of debate and conjecture.

### Other Lipid Reduction Therapies

There are several other classes of agents, including the fibrates, resin absorption inhibitors, ezetimibe, and niacin, that are available to treat lipid disorders. These agents are used as monotherapy and also in combination with statin therapy. This paper will discuss the pharmacology and clinical usefulness of two of them, ezetimibe, a cholesterol absorption inhibitor, and niacin, a B-vitamin.

### Ezetimibe<sup>4</sup>

Ezetimibe has been marketed in combination with simvastatin as Vytorin®, and also as Zetia® for use as monotherapy or to be taken along with other therapy such as other statins or even other lipid reducing agents.

### Mechanism of Action

Ezetimibe has a completely different mechanism of cholesterol lowering than do the statins. Ezetimibe reduces cholesterol by inhibiting cholesterol absorption in the intestines. Ezetimibe targets the NPC1L1 sterol transporter; located in the brush border epithelium of the small intestine.<sup>22</sup> Inhibition of this sterol transporter reduces intestinal absorption of cholesterol by 54%. This reduced cholesterol absorption leads to a reduction of intestinal cholesterol being transported into the liver, lowering hepatic cholesterol.<sup>22</sup> Lowering of hepatic cholesterol stimulates the clearing of cholesterol from the blood, with this final mechanism being similar to the mechanism of action with the statins.

### Effects on Lipid Levels

This action by ezetimibe results in a noticeable improvement in the serum lipids, with the total cholesterol reduced by 13%, the LDL-C by 19%, triglycerides reduced by 8%, and with the HDL-C increased by 3%.<sup>22</sup> Since this mechanism is completely different from the cholesterol reduction of the statins, the effects of ezetimibe are additive to statin effects in the reduction of cholesterol fractions.<sup>22</sup> Similar effects are also seen when ezetimibe is combined with fenofibrate.<sup>22</sup>

### Niacin<sup>5,6</sup>

Niacin, or nicotinic acid, is a B vitamin with cholesterol lowering properties. It has enjoyed varying levels of interest for its usefulness in managing lipid disorders. Its popularity appears to be on the rise, mainly because of suggestive results from the ARBITER-6 HALTS study, which was discussed previously. Whether this surge in popularity will turn out to be justified will hinge on the results of the AIM-HIGH study, now in progress, which will compare simvastatin/niacin (long acting) vs. simvastatin and placebo for the prevention of cardiovascular events.<sup>33</sup>

### Mechanism of Action

In spite of its use for the treatment of hyperlipidemia for over 50 years, the actual mechanism whereby niacin affects lipid levels is not clear. It is not related to its effect as a B vitamin.

### Effects on Lipid Levels

Niacin has noticeable effects on all of the significant lipid values. Also, the pattern of lipid effect is related to the dose level of niacin administered, with an increase in HDL-C beginning at lower doses and increasing with higher doses. Lowering of LDL-C, however, requires much more substantial doses, usually in the 1500–3000 mg range.<sup>34</sup> While the expected effects will vary with the preparation used and the individual patient, the pattern of change in the lipid fractions include, for the 1000 mg dose, an increase in the HDL-C of about 10%–15%, a 20%–25% reduction in triglycerides, along with insignificant effect on the LDL-C. At the 2000 mg daily dose, the HDL-C increase is about 20–30%, along with a 25%–30% reduction in triglycerides, and with about a 20% reduction in LDL-C. Lp(a) is reduced by 9% at 1000 mg up to 32% at the 2000 mg dose.<sup>34</sup> Higher doses, even up to 3000–4000 mg have been used, with greater reductions in LDL-C, but they are not commonly used now that the statins are available, and because of the profound levels of side effects that one can see with higher dose niacin.

### Considerations about Combination Lipid Therapy

There is increasing interest in combinations of lipid lowering agents of different classes to treat complex hyperlipidemia. Combination therapy is widely used in treating many other disorders, such as multiple agents to lower blood pressure or several different antibiotics to treat infections. Since hyperlipidemia is different than hypertension and infections, we cannot safely assume that combination therapy with different lipid lowering classes will be safe and beneficial. Medicine is scientific not logical. Therefore, we should need scientific studies rather than intuition to drive our therapeutic decisions. The lesson of torcetrapib is very important to remember. Torcetrapib was a CETP inhibitor that produced increases in HDL-C of about 72% coupled with a further reduction of about 25% in LDL-C, when it was added to atorvastatin therapy. It was assumed that these striking effects on these important lipid fractions would drastically reduce cardiac disease. In fact, the addition of torcetrapib produced significant increases in MI and cardiac mortality.<sup>7</sup> therefore, we need to be certain that combining two or more lipid reducing agents is safe and furthermore, that it reduces cardiac events rather than just improving indirect markers like lipid values or arterial intima thickening.

Combination therapy with ezetimibe to lower LDL-C further than with maximum statin therapy has been discussed earlier in this paper. It will remain unknown until the IMPROVE-IT trial is reported, as to whether this combination offers further events reductions over statin therapy. Aggressive lowering of LDL-C into the range of 50–55 mg/dl with rosuvastatin therapy alone produced significant events reductions in the JUPITER study, so we should maximize our statin therapy initially before adding a secondary LDL-C lowering agent. High dose niacin, in doses of 2500 mg or more, or resin binding agents like cholestyramine or colestipol can be added to high dose statin therapy in very difficult to control patients. However, this additional therapy is also unproven to reduce events and frequently has unacceptable side effects.

Combination therapy with niacin to lower elevated triglycerides is attractive to many practitioners. However, caution here is also in order. While elevated triglycerides add to the risk of elevated LDL-C in patients that are not on statin therapy, secondary analyses of several of the statin trials indicate that lowering elevated LDL-C with statin therapy eliminates the risks of elevated triglycerides.<sup>8,9</sup> Other studies have examined whether elevated triglycerides are actually an independent risk factor for increased cardiac events and have determined that they are not a true risk once the other abnormal lipid fractions like lower HDL-C have been accounted for.<sup>10,11,12</sup> Therefore, without at least strong evidence that lowering elevated triglycerides in addition to statin therapy actually reduces events, I recommend aggressive LDL-C lowering with maximal statin therapy and using low-fat, low carbohydrate diet to reduce triglycerides.

Combination therapy with niacin to increase low HDL-C is the most popular and attractive target for niacin therapy as added onto statin therapy. Also, several studies have shown that, in contrast with elevated triglycerides, low HDL-C remains a risk factor for cardiac events even with most traditional levels of statin therapy.<sup>13,14</sup> The one exception was from a recent secondary analysis from the JUPITER study, which lowered LDL-C levels down to the 50–55 mg/dL range. In that study, super lowering of LDL-C appears to have eliminated the additive risk of low HDL-C.<sup>15</sup>

### Combination Therapy

1. Statin is a selective HMG-CoA reductase inhibitor and causes a decrease in intracellular cholesterol levels and an increased clearance of LDL cholesterol in plasma.
2. Ezetimibe is a selective cholesterol absorption inhibitor, which potently and selectively prevents absorption of cholesterol through the intestinal wall. Since decrease in LDL receptors and HDL cholesterol is observed in hyperlipidemia, the use of both Statin and Ezetimibe in combination produces additive effects in hyperlipidemia.
3. Statin when used in combination with Ezetimibe causes manifold reduction in LDL cholesterol levels as compared to double the dose of the individual drug when used alone.

### Coronary Heart Disease (CHD)

Coronary heart disease (CHD) risk increases with age.<sup>16,17</sup> Despite this, lipid-lowering therapies are significantly under-utilized in patients > 65 years old.<sup>18,19</sup>

Raised cholesterol levels are a significant risk factor for the development of CHD, particularly if other known risk factors such as smoking, diabetes, hypertension and obesity are also present.<sup>20</sup> Lowering concentrations of total cholesterol and low-density lipoprotein cholesterol (LDL-C), raising high-density lipoprotein cholesterol (HDL-C)

can reduce the risk of cardiovascular events, and in high-risk patients, the cardiovascular morbidity and mortality. Statins are the current cholesterol-lowering drugs of choice for both primary and secondary prevention of CHD. They are more effective at lowering LDL-C than other classes of drugs and reduce coronary events, all cardiovascular events, and total mortality. Coronary heart disease treatment with HMG-CoA reductase inhibitors has been very successful. There is increasing interest in adding other lipid lowering therapy, primarily as additional therapy onto HMG-CoA reductase therapy<sup>20-23</sup>.

#### **Chronic Kidney Disease (CKD)**<sup>24,25</sup>

Chronic Kidney Disease (CKD) is a condition that causes slow loss of kidney function over time, taking months or years to develop. CKD is associated with an increased risk of heart disease; yet prevention of heart disease in patients with CKD continues to be a less researched area. Increased cholesterol levels serve as the prime cause for vascular events that ultimately result in heart disease. LDL cholesterol or 'bad cholesterol' is the worst agent responsible for the pathology. A number of drugs are available to fight high cholesterol levels. Statins are the most effective drugs available for reducing LDL levels, and work by inhibiting key enzymes in the synthesis of LDL. Simvastatin is a commonly used statin. Another drug called ezetimibe, which aids in fighting bad cholesterol, works by inhibiting the absorption of cholesterol in the small intestine. chronic kidney disease reduced the incidence of angioplasty or and of major diseases affecting the heart or blood vessels such as heart attack (myocardial infarction) and stroke. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease.

#### **Diabetes type 2**<sup>26,27</sup>

Ezetimibe is the first agent of a novel class of selective cholesterol absorption inhibitors and can be applied alone or in combination with statins in the treatment of type 2 diabetes with concomitant hyperlipidemia. Ezetimibe cannot only reduce the blood lipid but improve the glucose metabolism in type 2 diabetes patients. Animal experiments reveal ezetimibe can reduce the fasting insulin and improve the high-lipid induced impaired glucose tolerance (IGT) in diabetic rats with insulin resistance, but the specific mechanism is still unclear.

#### **Atherosclerosis**

Ezetimibe along with statins shows the better impact in the treatment of Atherosclerosis.

### **Conclusion**

While the temptation to add secondary agents like ezetimibe or niacin to statin therapy can be alluring, practitioners should remember the questions that we have discussed here. Adding either of these secondary agents has not been proven to reduce cardiac events in this add on role. They may be beneficial, but again they may not be. What can be said is that adding them will increase the cost of therapy (particularly for ezetimibe) or may significantly increase the risk of adverse effects, like the prominent itching and skin discomfort from niacin. With definitive research in progress, it is prudent for practitioners to avoid starting these therapies until clear benefit has been demonstrated. Ezetimibe/simvastatin provided additional lipid-modifying benefits over atorvastatin monotherapy at the recommended usual starting and next highest doses in patients with type 2 diabetes. Both treatments were generally well tolerated.

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