COMBINATION THERAPY IN DYSLIPIDEMIA

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Introduction

Hypercholesterolemia plays a key role in the development and progression of atherosclerosis and is a proven risk factor for coronary heart disease (CHD.)1. Therapeutic interventions aimed at lowering cholesterol levels both in primary and secondary prevention show a clear reduction in the incidence of CHD and stroke. 2Although widely used in lipid lowering therapy, HMG CoA reductase inhibitors (even when administered at high doses) are frequently insufficient to achieve guideline-recommended low-density lipoprotein cholesterol (LDL-C) goals for many patients with hypercholesterolemia in everyday clinical practice. According to a recent study, a large proportion of high-risk hyperlipidemic patients receiving statins alone are not at goal even when physicians were free to use any statin and titrate according to their professional judgment. The more aggressive cholesterol treatment goals proposed by the revised guidelines call for a more effective approach to maximize the cardiovascular benefits associated with lower LDL-C levels. 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 liver4. This results in dual inhibition of both sources of cholesterol provides significantly greater LDL-C reduction and subsequent goal attainment. Ezetimibe can be effectively co-administered with any dose of any statin; indeed the benefits are consistent across the statin brand and dose subgroups and compared with single inhibition of cholesterol production, afforded by statins alone, provides consistently greater reductions in LDL-C through dual inhibition of both cholesterol production and absorption. The single product of ezetimibe/simvastatin provides superior LDL-C lowering efficacy with improved LDL-C goal attainment.5 In early June, the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration (FDA), on which we serve, met to consider marketing applications for the new molecular entities alirocumab and evolocumab on the basis of their ability to lower low-density lipoprotein (LDL) cholesterol levels and their effects on other lipid fractions in patients at risk for cardiovascular disease. These first-in-class medications are fully humanized monoclonal antibodies that inactivate proprotein convertase subtilisin–kexin type 9 (PCSK9). That inactivation results in decreased LDL-receptor degradation, increased recirculation of the receptor to the surface of hepatocytes, and consequent lowering of LDL cholesterol levels in the bloodstream. Statins, by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, similarly act by increasing LDL-receptor expression. This shared LDL cholesterol–lowering mechanism, combined with data on cardiovascular events from genetic studies of persons with PCSK9 gain- or loss-of-function mutations, has led to optimism regarding the potential – but as yet unproven – cardiovascular benefits of these agents.

Treating two sources of cholesterol: co-administrating ezetimibe together with statin

Statins (eg, fiuvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, and rosuvastatin) deliver only single inhibition of cholesterol production in the liver by blocking HMG-Co A reductase, the rate-limiting step in cholesterol synthesis, but do not impact significantly intestinal cholesterol absorption. As a result, hepatocytes become depleted of cholesterol

and respond by increasing LDL-C clearance from the blood (via upregulation of hepatic LDL-C receptors) and decreasing entry of LDL-C into the circulation. These actions, in turn, result in the lowering of plasma LDL-C levels. Of note HMGCoA reductase inhibitors could target also cholesterol synthesis in the ileum; therefore reduced cholesterol biosynthesis in the small intestine by statins may also contribute to the reduction of plasma cholesterol concentrations.6Ezetimibe added to a statin has the potential to lower cholesterol by dual inhibition of both cholesterol absorption and cholesterol synthesis. Adding ezetimibe to ongoing statin therapy led to a substantial additional reduction in LDL cholesterol levels, facilitating attainment of NCEP goals. In patients with hypercholesterolemia not at goal on statin therapy alone, the Ezetimibe Add-On to Statin for Effectiveness (EASE) trial Denke et al demonstrated that co-administering ezetimibe (10 mg) with any dose of statin reduced LDL-C levels by an additional 25%, compared with the usual 6% attained by doubling the statin dose and improved LDL-C goal attainment from 20% on statin monotherapy to 71% vs 18.9% on statin alone, $p < 0.001$. (Figures 1 and and 2).7 The benefits were consistent across the statin brand and dose subgroups, in particular association of ezetimibe with atorvastatin (10–80 mg), fluvastatin (20–80 mg), lovastatin (20–80 mg), pravastatin (10–80 mg), simvastatin (10–80 mg) was studied8. Ezetimibe when co-administered with a statin was significantly better than placebo in increasing high-density lipoprotein cholesterol (HDL-C) and reducing triglycerides, non-HDL-C, and apolipoprotein B ($p < 0.001$ for all between-treatment differences). The superior reduction in LDL-C with ezetimibe compared with placebo was consistent across all ages, in men and women, and all ethnicities. Patients with diabetes or metabolic syndrome (including those with or without diabetes) who were randomized to ezetimibe had superior reduction in LDL-C compared with placebo. The superior LDL-C reduction with ezetimibe was consistent when analyzed by statin brand and statin dose. Other lipid parameters statistically improved with the addition of ezetimibe were: ratios of LDL-C/HDL-C, of total cholesterol/HDL-C and non-HDL-C. Finally C-reactive protein, a non-specific inflammatory marker associated with cardiovascular risk, was further reduced by 12%.

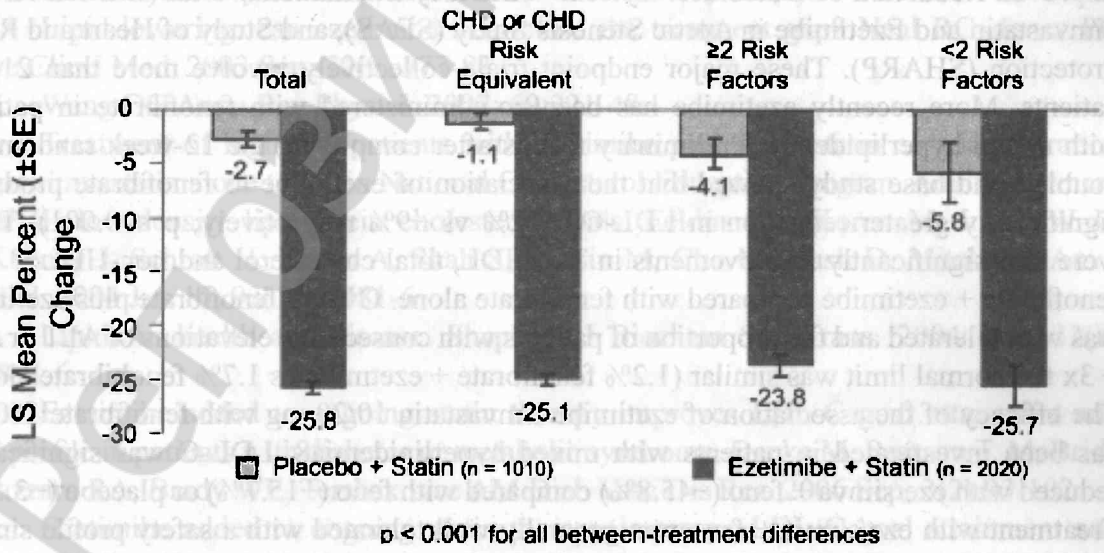

Fig.1 – Ezetimibe Add-On to Statin for Effectiveness study: percentage changes in LDL-C overall and by NCEP CHD risk category (n = 3030). Drawn from data of Pearson et al. (2005).

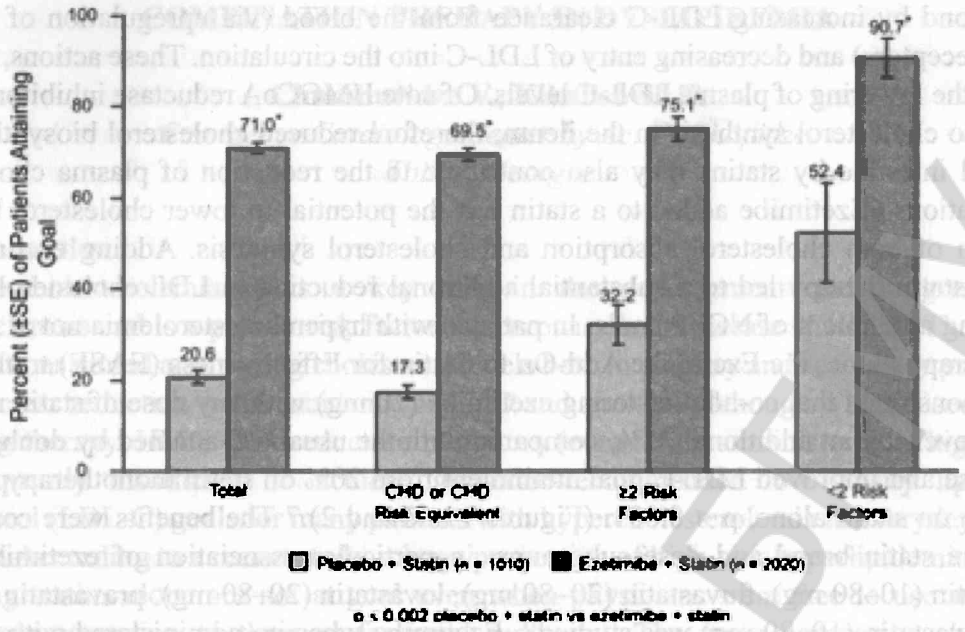

Fig.2 – Ezetimibe Add-On to Statin for Effectiveness study: LDL-C goal attainment for patients (n = 3030) not at goal at baseline. Drawn from data of Pearson et al. (2005).

Ezetimibe, dyslipidemia and cardiovascular outcomes: future developments

Although treating two sources of cholesterol through dual inhibition provides superior LDL-C lowering efficacy with improved LDL-C goal attainment, one key clinical question remains to be addressed: Do the lower LDL-C levels achieved with dual inhibition of cholesterol production and absorption ultimately translate into reduced cardiovascular or renal events and a slower rate of progression of atherosclerosis? This question is currently being assessed in several major cardiovascular outcomes studies, including Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE), Improved Reduction of Outcomes: Vytorin™ Efficacy International Trial (IMPROVE IT), Simvastatin and Ezetimibe in Aortic Stenosis Study (SEAS), and Study of Heart and Renal Protection (SHARP). These major endpoint trials collectively involve more than 21,000 patients. More recently ezetimibe has been co-administered with fenofibrate in patients with mixed hyperlipidemia. Preliminary results after completing the 12-week randomized double-blind base study showed that the association of ezetimibe to fenofibrate produced significantly greater reduction in LDL-C (−22% vs −9% respectively; $p < 0.001$). There were also significantly improvements in TG, HDL, total cholesterol and non-HDL-C with fenofibrate + ezetimibe compared with fenofibrate alone. Overall fenofibrate plus ezetimibe was well tolerated and the proportion of patients with consecutive elevations of ALT or AST > 3x the normal limit was similar (1.2% fenofibrate + ezetmibe vs 1.7% fenobibrate alone). The efficacy of the association of ezetimibe/simvastatin 10/20 mg with fenofibrate 160 mg has been investigated in patients with mixed hyperlipidemia8. LDL-C was significantly reduced with eze/simva + feno (−45.8%) compared with feno (−15.7%) or placebo (−3.5%). Treatment with eze/simva + feno was generally well tolerated with a safety profile similar to the eze/simva and feno therapies. Further studies are warranted to investigate the role of ezetimibe and fibrates in mixed dyslipidemia. Patients with existing cardiovascular disease and persistently high LDL cholesterol levels despite high-intensity statin therapy also have important unmet medical needs. For this much larger population, the FDA must weigh the benefits of early approval against the possibility that the drugs will be substituted for maximally tolerated statins, even though there's much better evidence of statins'

clinical benefit. The proposed labeling for the PCSK9 inhibitors would support their use in patients unable to take statins — a matter of concern, since statin intolerance appears to be overdiagnosed (e.g., 70% of patients who were considered unable to take statins in blinded alirocumab studies tolerated 20 mg of atorvastatin daily for 24 weeks). Although unlikely, an additional theoretical concern is that widespread availability of PCSK9 inhibitors might prompt patients enrolled in ongoing end-point trials to receive the medications outside the protocol, thereby compromising the trials' integrity.

Conclusions

A wide therapeutic gap exists between target LDL-C levels and LDL-C levels typically achieved in actual clinical practice – a gap that will certainly widen with traditional therapy of single inhibition in light of recent amendments to the NCEP ATP III guidelines. The new aggressive cholesterol treatment goals call for a more advanced therapeutic approach to maximize the cardiovascular benefits associated with lower LDL-C levels. One logical approach is to target both cholesterol production in the liver and absorption in the intestine. By administrating ezetimibe/simvastatin as a single tablet or co-administering ezetimibe together with any dose of any statin, we can expect superior LDL-C-lowering efficacy and a substantially greater proportion of patients achieving or getting below LDL-C treatment goals. Treating two sources of cholesterol through dual inhibition should therefore be considered as a more advanced therapeutic option for all hypercholesterolemic patients whose LDL-C levels are not appropriately controlled approximately 2-3 months after initiating statin monotherapy. Trials focusing specifically on long-term cardiovascular outcomes and safety are under way, and the results of these trials in the next several years will be very important in determining whether PCSK9 inhibitors become a more common part of the regimen for treating high cholesterol.

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