

Extended release Niacin vs. Ezetimibe: Results of the ARBITER 6-HALTS Trial

Introduction: On November 15, 2009 the New England Journal of Medicine released online the results of the ARBITER 6-HALTS trial to coincide with presentations at the American Heart Association Scientific Sessions. **In this comparative-effectiveness trial the authors conclude that combining chronic statin monotherapy with a treatment [i.e., extended-release niacin (NIASPAN)] intended to raise high-density lipoprotein cholesterol (HDL-C) is more effective at reducing carotid intima-media thickness (IMT) than an adjunctive therapy [ezetimibe (ZETIA)] utilized to further lower low-density lipoprotein cholesterol (LDL-C).**

Methods: A total of 363 patients with known coronary heart disease or a coronary heart disease risk equivalent (e.g., diabetes, 10-year Framingham risk score of 20 percent or more, etc.) on long term monotherapy with statins were enrolled in this 14-month study. Subjects were required to have LDL-C laboratory values below 100mg/dl and HDL-C levels below 50mg/dl for men and 55mg/dl for women. Study subjects were then randomly assigned to receive either extended-release niacin (target dose = 2,000mg/day) or ezetimibe 10mg daily. Of note, 75 percent of patients reached the 2,000mg target dose for extended-release niacin and both drugs were given in an open-label format. The primary endpoint of the study was to measure the difference between the two groups in the change of carotid IMT from baseline to 14 months. Secondary endpoints included: Change in lipid values, incidence of major cardiovascular events (e.g., heart attack, heart revascularization, hospital admission for acute coronary syndrome, and death from coronary heart disease), discontinuation of study drug due to adverse effects, and health-related quality of life.

Results: The study was terminated early because of a difference in efficacy between the two combination therapies. As a consequence, the 14-month endpoint data for only 208 patients (57 percent of the total enrollment) were available for evaluation. Regarding the primary endpoint, niacin was found to be more effective than ezetimibe at reducing carotid IMT at both the eight-month and 14-month follow-ups. It was found that there was a significant reduction in carotid-IMT from baseline with niacin, whereas there was no change noted with ezetimibe. In addition, ezetimibe was shown to be more effective at lowering LDL-C (i.e., 19.2 percent reduction); while niacin was more effective at raising HDL-C (i.e., 18.4 percent increase). A significantly larger number of patients experienced the composite outcome of major cardiovascular events in the ezetimibe group (5 percent in comparison to the niacin group (1 percent). There was no significant difference in the two therapies in both the number of subjects who left the study due to adverse effects and health care-related quality of life measures.

Discussion: The use of statin therapy to reduce levels of LDL-C in patients who are at high risk for cardiovascular events has been shown to reduce these events by 30 to 40 percent. The problem lies in the fact that many patients continue to be at increased cardiovascular risk in spite of chronic statin monotherapy. One approach to this clinical dilemma is to further lower LDL-C by increasing statin dosing, possibly to an intolerable level, or to add additional therapies (e.g., ezetimibe) that also work to decrease LDL-C. A second approach would be to target decreased HDL-C levels with the addition of other agents such as niacin. The ARBITER 6-HALTS trial was designed to address this very question. The results of this study – obtained in a modest sample of 208 patients, followed for 14 months – show a clear superiority of niacin over ezetimibe in decreasing carotid IMT.

Some of the possible methodological concerns that members of the medical community have with this study include: a) early termination of the study by the data and safety monitoring board which can result, among other factors, in an overestimation of treatment effect; b) use of carotid-IMT measurement as a surrogate marker for clinical endpoints; c) relatively small sample size; d) a study design that favored niacin over ezetimibe; and e) support from pharmaceutical manufacturer ABBOTT (maker of NIASPAN) to finance the study. More data can be expected in the next few years on this important issue. There are two ongoing studies investigating clinical endpoints with ezetimibe, SHARP, due in 2011 and IMPROVE-IT in 2012. There are also two studies looking at outcomes with niacin, AIM-HIGH in 2011 and HPS2-THRIVE in 2013.

Lastly, this cannot be good news for pharmaceutical giant MERCK and its product, VYTORIN, which had to endure fairly intensive media scrutiny following the release of the ENHANCE trial in 2008. Results of the ENHANCE trial showed that after two years of treatment, combination therapy simvastatin/ezetimibe (VYTORIN) was no more effective at reducing progression of carotid IMT than simvastatin alone. The ENHANCE trial was an international, randomized, double-blind, controlled trial that lasted two years and enrolled over 700 patients. The sponsors of the study, MERCK and Schering-Plough, were criticized by a U.S. House Committee for their two year delay in making the results available. In addition, many questions were raised about the use of surrogate makers for clinical endpoints (i.e., VYTORIN reduced LDL-C levels by 58 percent vs. 41 percent reduction with simvastatin alone), possible increased risk of liver toxicity, and the true value that the branded combination product VYTORIN (~ \$3.03 per tablet) actually provided over generic simvastatin (~ \$0.60 per tablet).

Conclusion: The results available to date would suggest that the use of statins to reduce LDL-C to target levels with subsequent addition of a drug (e.g., niacin) to raise HDL-C levels rather than a drug to further lower LDL-C levels is a more effective treatment for patients at an elevated cardiovascular risk level. Additional studies should help to further clarify the role of niacin as an adjunct to statin monotherapy in providing residual cardiovascular risk reduction.

References:

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