

Medicare Part D pharmacy updates: Results of the ARBITER 6-HALTS trial

In November 2009, *The New England Journal of Medicine* released results of the ARBITER 6-HALTS comparative-effectiveness trial. The authors concluded that combining chronic statin monotherapy with a treatment (e.g., 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[®]]) used to further lower low-density lipoprotein cholesterol (LDL-C).

Methods: The 14-month study involved 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) on long-term monotherapy with statins. Subjects were required to have LDL-C laboratory values below 100 mg/dl and HDL-C levels below 50 mg/dl for men, and 55 mg/dl for women. Subjects were randomly assigned to receive either extended-release niacin (target dose = 2,000 mg/day) or 10 mg ezetimibe daily.

Seventy-five percent of the participants reached the 2,000 mg 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. For 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. A significant reduction in carotid-IMT from baseline with niacin was found, whereas no change was noted with ezetimibe.

In addition, ezetimibe was shown to be more effective at lowering LDL-C (a 19.2 percent reduction), while niacin was more effective at raising HDL-C (an 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). Lastly, 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-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. 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:

- Early termination of the study by the data and safety monitoring board which can result, among other factors, in an overestimation of treatment effect
- Use of carotid-IMT measurement as a surrogate marker for clinical endpoints
- Relatively small sample size
- A study design that favored niacin over ezetimibe
- Support from pharmaceutical manufacturer Abbott Laboratories (maker of NIASPAN) to finance the study. There are two ongoing studies investigating clinical endpoints with ezetimibe and two studies looking at outcomes with niacin.

This cannot be good news for pharmaceutical giant Merck and its product, VYTORIN[®], which endured 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 publishing the results. In addition, many questions were raised about the use of surrogate makers for clinical endpoints (e.g., VYTORIN reduced LDL-C levels by 58 percent vs. a 41-percent reduction with simvastatin alone), the possible increased risk of liver toxicity, and the value that the branded combination product VYTORIN (about \$3 per tablet) actually provided over generic simvastatin (about \$0.60 per tablet).

Conclusion: The results 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 further clarify the role of niacin as an adjunct to statin monotherapy in providing residual cardiovascular risk reduction.