ENHANCE Study

By Kathy Tang, 2014 PharmD Candidate; Michael E. Stuart, MD; and Sheri A. Strite

Introduction

The ENHANCE study analyzed the efficacy of combining simvastatin with ezetimibe to reduce the progression of atherosclerosis in patients with a family history of hypercholesterolemia. The progression of atherosclerosis is measured by the thickness of the intima-media located in the carotid and femoral arteries. Patients with familial hypercholesterolemia have a higher risk of premature coronary artery disease; in addition, their intima-media thickens at an increased rate. By using simvastatin with ezetimibe, two compounds with different mechanism of action, the progression of atherosclerosis was expected to decrease. The goal of the study was to show that ezetimibe and simvastatin will decrease the progression of atherosclerosis determined by measuring the thickness of the intima-media.

The study is a prospective, double-blind randomized, 24 month trial comparing the two study groups: 80 mg simvastatin with placebo or 80 mg simvastatin with 10 mg ezetimibe. Patients are assigned to each arm of the study by a computer generated code. The authors concluded that the intima-media thickness was not reduced by ezetimibe combined with high-dose simvastatin compared to simvastatin alone. The secondary LDL cholesterol and C-reactive protein were reduced significantly, but the differences between the two groups were not significantly different.

Results

The primary outcome results for the study was the change in the baseline measurement of the intima-media thickness in the two study groups. The results for the simvastatin therapy group were 0.005 ± 0.0037 mm and the simvastatin-ezetimibe therapy group was 0.0111 ± 0.0038 mm. P value for this analysis was p = 0.29, indicating no statistical significance. Data was also obtained from the secondary outcome measurements: regression of the mean carotid-artery intima media thickness in 44.4% of the patients in the simvastatin-only group and 45.3% in the simvastatin-ezetmibe group; new plaque formation greater than 1.3 mm in the intima-media thickness was seen in 2.8% of the simvastatin-only group and 4.7% in the combined therapy group. The study concluded that there were no significant differences in outcome between the two groups at both end-points; therefore, ezetimibe and simvastatin is not a recommended therapy.

Conclusion

Overall the study concluded that high-dose simvastatin combined with ezetimibe 10 mg does not reduce intima-media thickness more than patients treated with simvastatin 80mg alone. Weaknesses of the study include the two study populations having differences in past medical history, cardiovascular complication, and body mass index. These differences may be due to the randomization process as each group were stratified by study site. For future studies it is ideal to enroll patients with similar medical history and cardiovascular complications to obtain a better comparison. Additional flaws in the study include the inability to accurately measure the change in arteriosclerosis progression in patients enrolled. The data obtained for the population study reflected no significance in using either treatment therapy; however, this may be due to limitations such as differences in past medical history and body mass index.

The study population may not have been the ideal candidates for this study, which may have caused difficulty in finding significant differences between the two groups. Patients with New York Heart Association class III or IV congestive heart failure cardiac arrhythmia, angina pectoris, or recent cardiovascular events were excluded from the study. These exclusion criteria excluded a population group that may have benefited from this regimen. The general population would reflect a variety of cardiovascular diseases, which were exclusion criteria for the participants.

ENHANCE is a prospective, randomized, double-blind, active comparator, multicenter study. The study has threats in the variation in the study population and does not represent the general population. Moreover, a more comprehensive study population may provide further insights on the effectiveness of simvastatin and ezetimibe combined. Further research and studies on the effectiveness of simvastatin and ezetimibe is needed to determine the usefulness of this treatment combination. The current conclusion from ENHANCE is that ezemitibe and simvastatin did not reduce intima-media thickness more effectively than those who take high-dose of simvastatin.

Overall Grade: BU

A grade of BU is given to the study for its uncertain applicability to the general population. Study contains threats such as unknown blinding of accessors and preventative measures to protect the blinding of the accessors during study visits. Study population was not representative of the general population.

Element	Criteria	Comments
Study Design Assessment	Is the design appropriate to the research question? Is the research question useful? • For efficacy, use of experimental study design (meaning study subjects and others were not allowed choice in determining interventions) • Clinically significant area for study (morbidity, mortality, symptom relief, functioning and health-related quality of life) and reasonable definitions for clinical outcome such as response, treatment success or failure • If composite endpoints used, reasonable combination used - and used for safety if used for efficacy	The ENHANCE study was designed using a double-blind placebo, controlled randomization study. Threat: Thickness of intima-media may not be an effective surrogate to determine progression of the atherosclerosis.
Internal Validity Assessment	Can bias, confounding or chance explain the study results? • Ensure prespecified and appropriate 1) research questions, 2) populations to analyze, 3) outcomes, 4) group assignment methods, 5) study conduct methods, 6) analysis methods, and 7) level for statistical significance	Threat: The study assumes lower LDL levels resulted in decreased intima-media thickness. Threat: Subjects analyzed in the study are not homozygous for familial hypercholesterolemia and have cardiovascular disease. These patients may have better results than the healthier subjects enrolled in the study.
Selection Bias	• Groups are appropriate for study, of appropriate size, concurrent and similar in prognostic variables • Methods for generating the group assignment sequence are truly random, sequencing avoids potential for anyone affecting assignment to a study arm and randomization remains intact • Concealment of allocation strategies are employed to prevent anyone affecting assignment to a study arm	Randomization occurred after the end of the run-in period of 6 weeks. The groups were randomized based on a computer-generated code. Patients were assigned to each group based on a 1:1 ratio. Each group was stratified based on the clinic site. Threat: The exclusion criteria for the subjects were stringent and not reflective of patients with familial hypercholesterolemia. Patients homozygous for hypercholesterolemia were excluded and patients with specified cardiovascular disorders. This is not reflective of the general population. Threat: The combined-therapy group differed in medical history. The ezetimibe-simvastatin group had an increased number of subjects with hypertension and fewer subjects with myocardial infarction. Threat: The body mass index (BMI) was significantly higher in the combined-therapy group than the simvastatin only group.
Performance Bias	• Double-blinding methods employed (i.e., subject and all working with the subject or subject's data) and achieved • Reasonable intervention and reasonable comparator used (e.g., placebo) • No bias or difference, except for what is under study, between groups during course of study (e.g., intervention design and execution, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations, measurement methods, study duration, etc.)	No differences in co-interventions were stated. Images of the intima-media thickness were all sent to the Academic Medical Center and thickness was measured using standardized equipment. Threat: Blinding of accessors were not specified in the study. Threat: It is unknown if the placebo dosage form matches the shape and form of ezetimibe. If the two dosage forms differ then bias may have occurred. Threat: This was a double-blinded study where the subject and the provider were blinded for the 24 month period. However, during the initial 6 week run-in period the study was single-blinded. Threat: The simvastatin with ezetimibe group had a higher compliance rate of 84% compared to the simvastatin only group 78%.
Attrition Bias	Zero or minimal missing data points or loss from randomization (e.g., approximately 5% with differential loss, or approximately 10% without differential loss) unless good ITT analysis (see ITT below)	Threat: The data for intima-media thickness of the common carotid artery was only 96.6% complete for measurements at the baseline and at the end of the study. Completeness of primary outcome data was 88% for patients with a minimum of one end-of-study visit. The lack of completeness of data can alter the potential outcome of the study.

About the Authors

Kathy Trang is a 2014 PharmD Candidate at the University of Illinois, Chicago College of Pharmacy. *Michael E. Stuart, MD* and *Sheri A. Strite* of Delfini Group are experts at systematic literature reviews. The chart template is adapted from "Delfini Group, LLC, Short Critical Appraisal Checklist: U."

Reference

1. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, De Groot E. Simvastatin with or without ezetimibe in familial hypercholesterolemia. New England Journal of Medicine 2008; 359:5, 529-533.

Assessment Bias	• Assessors are blinded • Low likelihood of findings due to chance, false positive and false negative outcomes (judgment call on statistical significance, including confidence intervals) • Non-significant findings are reported, but the confidence intervals include clinically meaningful differences • Intention-to-Treat Analysis (ITT) performed (all people are analyzed as randomized + reasonable method for imputing missing values which puts the intervention through a challenging trial or reasonable sensitivity analysis) • Use of modeling only with use of reasonable assumptions	Assessors were blinded. Threat: Confidence Intervals were not presented, but analysis of the p value measuring the intima-media thickness indicated that the finding may be due to chance. P values for the measurements of the intima-media thickness are greater than 0.1, which indicates the values are not of statistical significance. Threat: The analysis used to compare the two study groups at baseline was based on an intent-to-treat basis. For patients who discontinued the study early, a last-observation-carried-forward method was used; however, this method disregarded the improvement or progression of the patients' condition at the time of discontinuation. This is a potential cause of bias in the results.
Usefulness Assessment	Clinically significant area + sufficient benefit size = meaningful clinical benefit (consider efficacy vs effectiveness)	Threat: Overall the study demonstrated ezetimibe and simvastatin combined did not reduce atherosclerosis progression in patients with familial hypercholesterolemia. Further studies need to be performed to prove the effectiveness of this therapy to be used in a clinical setting. Threat: The study was set at a power of 90% to detect a difference of 0.05 mm, which required a minimum of 325 subjects in each study group. Only 320 patients in the simvastatin group and 322 patients in the ezetemibe-simvastatin combination group completed the study. Patients who discontinued the study were analyzed using last-observation-carried-forward, which may generate bias. Threat: The study is geared towards people with difficult to manage and higher levels of cholesterol; however, patients with major cardiovascular events were excluded.
External Validity	How likely are research results to be realized in the real world considering population and circumstances for care?	Threat: Due to the stringent exclusion and inclusion criteria, the study population does not reflect the general population of patients with cholesterol problem. Patients are excluded from the study if they have a history of heart conditions such as carotid stenting, homozygous familial hypercholesterolemia, and angina pectoris. The population does not reflect the general population of patients with familial hypercholesterolemia.
	Review n, inclusions, exclusions, baseline characteristics and intervention methods ? this is a judgment call.	
Patient Perspective	Consider benefits, harms, risks, costs, uncertainties, alternatives, applicability to which patients, adherence issues, potential for abuse, dependency issues and patient satisfaction	Threat: Patients may not benefit from using ezetimibe with simvastatin concomitantly. A decrease in intima-media thickness does not necessarily indicate reduced progression in atherosclerosis.
Provider Perspective	Satisfaction, acceptability, likely appropriate application and actionability (e.g., FDA approval, affordability, external relevance, circumstances of care, able to apply, tools available)	Despite the hope that the combination therapy will delay the progression of atherosclerosis, the study concludes that ezetimibe and simvastatin combined do not reduce atherosclerosis. The combination therapy is not a recommended treatment used by providers.

Delfini Evidence Grading Scale

Grade A Evidence: Useful
The evidence appears strong and sufficient to use in making health care decisions - no significant threats to validity were ascertained.

Grade B Evidence: Possibly Useful
The evidence appears potentially strong and is probably sufficient to use in making health care decisions - some threats to validity were identified

Grade B-U Evidence: Possible to uncertain usefulness
The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Health care decision-makers should be fully informed of the evidence quality.

Grade U Evidence: Uncertain
There is sufficient uncertainty that caution is urged regarding its use in making health care decisions. Delfini does not use such information to inform clinical decisions regarding efficacy