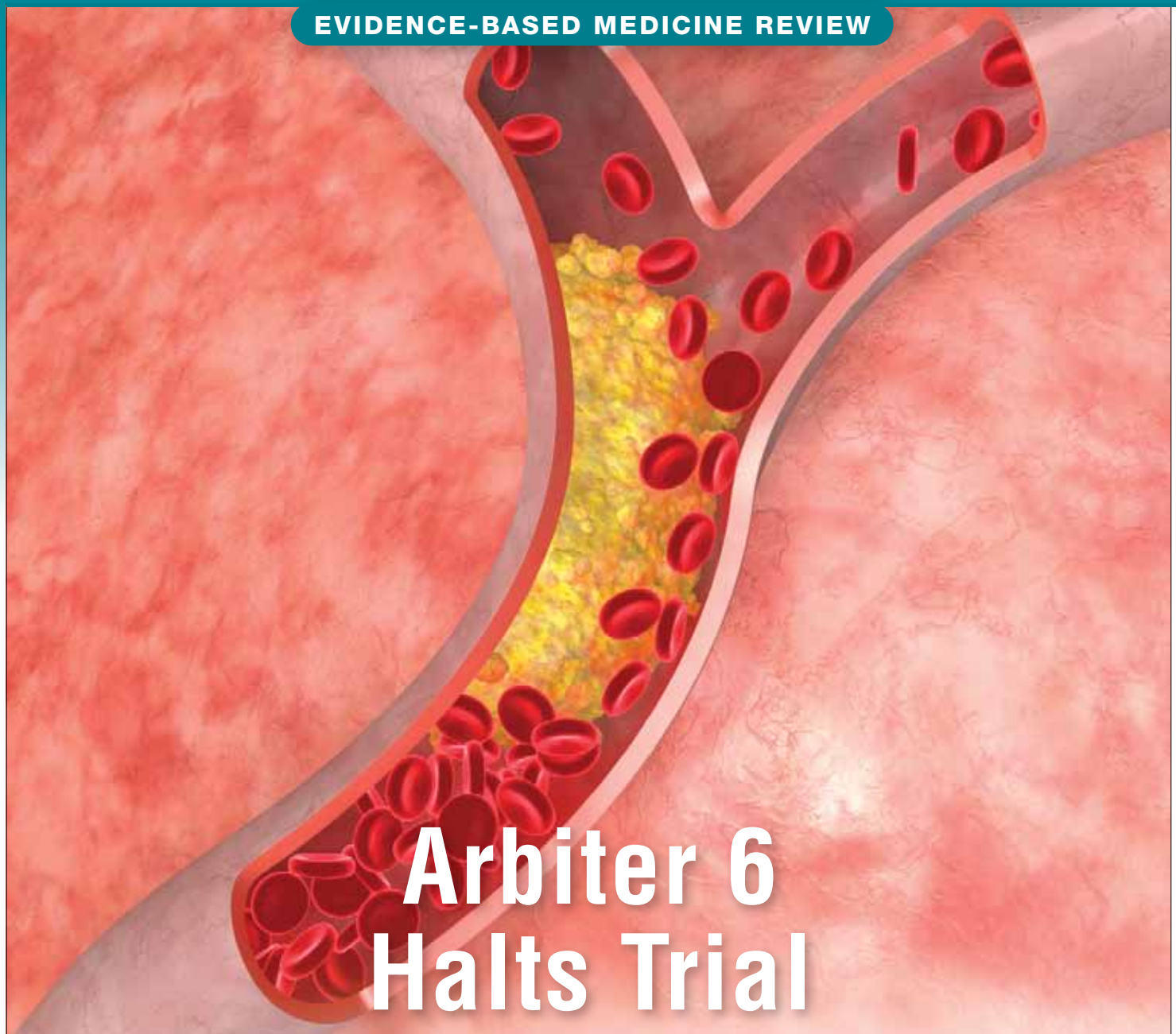

Arbiter 6 Halts Trial

by Melody Chien 2012 PharmD Candidate, Justin Yee 2012 PharmD Candidate, and Craig Stern, PharmD, MBA, FCPhA

Special thanks to Guest Editors from Delfini Group, LLC. Michael E. Stuart, MD and Sheri A. Strite

Introduction

The Arbiter 6 Halts trial was conducted to evaluate the efficacy of two statin combination therapies. The study compared niacin+statin versus ezetimibe+statin in order to evaluate which statin combination was more effective at slowing progression of atherosclerosis. The primary end point/outcome measure was carotid intima-media thickness (IMT), which researchers used as a surrogate marker.

Based on the results of a 14-month prospective, randomized, parallel-group, open-label study, authors concluded that using a combination of statin+niacin was a superior therapy compared to using ezetimibe+statin. The purpose of this evidence-based evaluation of ARBITER 6 HALTS is to determine if this new combination drug therapy is a viable and efficacious option for those patients who are not well controlled by statins alone.

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	ARBITER 6 HALTS trial was designed as an open-label randomized study designed to assess adjunct pharmacological treatment to reduce the risk of cardiovascular events in patients with coronary heart disease or risk equivalent. **THREAT:** The study used carotid intima-media thickness as a surrogate marker for atherosclerosis progression, but there could potentially be other outcomes, such as heart attack, stroke, and other various cardiovascular events, that could more accurately assess the progression of 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 open-label study design allows both researchers and participants to be aware of who was getting the different drug combinations which could have influenced results. **THREAT:** Of the 363 participants initially randomized, only 208 participants were analyzed at the 14 month premature termination of the trial. As a result, conclusions and study findings were based on only these participants.
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	**THREAT:** A small sample size was used and thus may not be reflective of the general patient population who may potentially receive this therapy. The study was conducted at two centers–Walter Reed Army Medical Center and the Washington Adventist Hospital. Computer-generated sequence of random numbers was used to allocate treatment groups. **THREAT:** Concealment of allocation strategies was not detailed by the study authors.
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.)	**THREAT:** This trial was not double-blinded, but instead an open label study (only endpoint evaluators and the sole ultrasonographer were blinded). Therefore, all others involved in the study were fully aware of which treatment arm to which patients were assigned. **THREAT:** Though both groups received an active medication, biases could have affected behavior based on perception of potential drug efficacy. **THREAT:** Because the two treatment arms received active drug, either niacin+statin or ezetimibe+statin, the study lacked a comparator group of either just statin therapy and/or placebo, which would have better determined true cardiovascular risk reduction.

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:** 9% of patients taking ezetimibe and 15% of patients taking niacin discontinued the medication mostly due to adverse drug effects. The drop out rate of the niacin group is almost double that of the ezetimibe group; thus, the niacin group is missing more data points for analysis, possibly misrepresenting positive or negative outcomes. **THREAT:** The loss of data, due to the drop out rate, threatens the internal validity of the study.
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	**THREAT:** This study was conducted using single-variable correlation coefficients which failed to take into account other variables other than carotid intima-media thickness. In addition the study performed post hoc analyses. Both these are quite sensitive to bias due to confounding. The primary investigators were not blinded; however, both assessors of the study and a single observer (the single ultrasonographer) were blinded. **THREAT:** Because the study was prematurely terminated, there is an increased likelihood for chance effects especially in a small study as well as an exaggerated/overestimated assessment of the potential benefit of niacin. **THREAT:** Not all randomized patients were accounted for in the analysis. Therefore this is not an ITT analysis. Only 208 (about two-thirds of the starting patient population) completed the study and were accounted for in final analyses.
Usefulness Assessment	☐ **Clinically significant area + sufficient benefit size** = meaningful clinical benefit (consider efficacy vs effectiveness)	**THREAT:** The trial failed to substantiate that statin adjunct therapy using niacin or ezetimibe was more effective than simply maintaining statin monotherapy and increasing the dosage/strength of the statin, and due to multiple threats to trial validity such as the primary outcome being a surrogate marker. In order to further strengthen study claims on the superiority of the statin + niacin adjunct therapy, additional trials evaluating clinical outcomes, such as MI or stroke, are necessary.
External Validity	**How likely are research results to be realized in the real world considering population and circumstances for care?** ☐ Review inclusions, exclusions, baseline characteristics and intervention methods. This is a **judgment call**.	**THREAT:** Because of numerous trial flaws that threaten internal validity, an evaluation of external validity is not warranted.
Patient Perspective	☐ Consider benefits, harms, risks, costs, uncertainties, alternatives, applicability to which patients, adherence issues, potential for abuse, dependency issues and patient satisfaction	Since the study showed an increase of reported cardiovascular events in the ezetimibe group, patients may be more inclined to decline initiating ezetimibe therapy. Although, trial findings appear to suggest that the niacin+statin combination is superior to ezetimibe+statin, there are uncertainties (biases mentioned earlier) as to the true superiority of the niacin+statin therapy; thus, other alternatives and patient specific variables should be considered prior to initiating therapy.
Provider Perspective	☐ Satisfaction, acceptability, likely appropriate application and actionability (e.g., FDA approval, affordability, external relevance, circumstances of care, able to apply, tools available)	All of the medications used in the trial are on the market and are currently FDA approved to treat dyslipidemia as monotherapy. **THREAT:** Due to numerous unanswered questions and potential threats from study design, clinical application of niacin+statin therapy cannot yet be recommended without conducting further trials to assess claims.

ARBITER 6 HALTS = Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol - 6 - HDL and LDL Treatment Stretegies in Atherosclerosis

Author's Results and Conclusion:

The final changes in LDL were -17.6±20.1 mg/dL and -10.0±24.5 mg/dL in the ezetimibe and the niacin groups respectively. The final changes in HDL levels were -2.8±5.7 mg/dL and 7.5±9.2 mg/dL in the ezetimibe and the niacin groups respectively. Primary outcome measurement evaluated the change in carotid intima-media thickness. Compared to ezetimibe, which had a -0.0007±0.0035 (p = 0.84) change in mean thickness, niacin had a -0.0181±0.0050 mm (p=0.001) change in mean thickness. More patients in the niacin+statin study arm withdrew from the study than those on ezetimibe+statin, mainly due to adverse drug effects. The authors concluded that the niacin+statin combination was superior to ezetimibe+statin due to the greater decrease in carotid media-intima thickness.

Reviewer's Conclusions:

The ARBITER 6 HALTS trial presents many claims in support of statin+niacin as a superior drug combination therapy to statin+ezetimibe combination therapy stating improved outcomes for patients with cardiovascular risk. Due to a number of threats to study validity, initializing statin+niacin therapy in the clinical setting has not been determined to be superior and thus, should not yet be considered standard of practice. Major downfalls of this trial include the open-label design, early termination of the study, loss of data points including differential loss and the lack of ITT analysis. While the open-label study design assures participants that they are receiving actual pharmacologic therapy, it creates a performance bias because each individual in fact knows what they are really getting which may influence study outcomes. The lack of ITT analysis weakens study claims that would be rather promising. Because the study size was rather small (363 participants), as each participant drops out, whether it is from adverse events or lack of compliance, there is a larger percentage of the total outcome placed on each patient, making it increasingly more possible for outcomes to be distorted by bias, rather than to be explained by treatment effects.

Additionally, both investigator and participant bias are potentially confounding factors. Although the reproducibility of carotid IMT is among the highest ever achieved in a clinical trial, a small number of participants completed the trial over a short time period (208 participants enrolled for a total of 14 months in a trial that was terminated early). This is certainly not enough to convince most that a statin+niacin combination is more effective for treating a disease state.

The recruited patient population is another study design that threatens external validity. Men and women with HDL levels less than 50 and 55 mg/dL, respectively, do not accurately represent the average patient population that would require a statin combination therapy. Patients with HDL levels this high are less likely to experience a cardiovascular event and may not require the drug therapy used in the trial. We should consider whether the drug therapies in question would have positive outcomes for individuals who have much lower HDL levels. Therefore, due to the number of threats to internal and external validity, asserting that using a statin+niacin drug combination is more efficacious and superior to a statin+ezetimibe combination cannot be corroborated.

Although the ARBITER 6 HALTS trial suggests a beneficial statin+niacin combo therapy, further research and trials are needed to fully evaluate the long-term potential and risk in using such statin combinations in treating cardiovascular disease.

Overall Grade: U = Uncertain in validity and usefulness

About the Authors

Melody Chien is a 2012 PharmD Candidate at the USC School of Pharmacy. Justin Yee is a 2012 PharmD Candidate at the USC School of Pharmacy.

Craig Stern, PharmD, MBA is president of ProPharma Pharmaceutical Consultants, Inc. and Chair of the CPhA Editorial Review Committee. Dr. Stern has no bias to disclose.

Guest Editors Dr. Michael E. Stuart 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

References

ARBITER Study Group. Allen J. Taylor et. al. "Extended-Release Niacin or Ezetimibe and Carotid Intima-Media Thickness (ARBITER HALTS-6)." *N Engl J Med* 361:2113-22, 2009 November 16.

Chart adapted from Delfini Group, LLC Short Critical Appraisal Checklist

Delfini Evidence Grading Scale
Grade A Evidence: Useful The evidence is strong and appears sufficient to use in making health care decisions – it is both valid and useful (e.g., meets standards for clinical significance, sufficient magnitude of effect size, physician and patient acceptability, etc.).
Grade B Evidence: Probably Useful The evidence appears potentially strong 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. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.
Grade U Evidence: Uncertain Usefulness There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.