ADVANCE Trial

by Sapna N. Patel, 2010 Pharm. D. Candidate, USC School of Pharmacy,
Sheri A. Strite, Michael E. Stuart, MD and Craig Stern, Pharm. D., MBA

Introduction

The ADVANCE trial (Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus, a randomized controlled trial) was conducted to evaluate the effectiveness of a fixed-dose of anti-hypertensive agents, indapamide and perindopril, in diabetic patients regardless of initial blood pressure levels or the use of other blood-pressuring agents. The ADVANCE trial has 2 main arms. This review focuses on the first arm of the ADVANCE trial. The complete results of the second arm focuses on evaluating the effectiveness of intensive glicazide MR therapy with goal of $HbA_{1c} \leq 6.5\%$. The complete results of the ADVANCE trial have yet to be released.

The primary outcome measures were composites of major microvascular and macrovascular events. Microvascular events described as major were new or worsening nephropathy, or retinopathy. Major macrovascular events included cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Secondary outcomes included all-cause mortality, cardiovascular death, major coronary event, total coronary events, major cerebrovascular events, and total cerebrovascular events. Authors concluded that daily usage of fixed combination perindopril and indapamide type 2 diabetic patients was well tolerated, required infrequent monitoring, and reduced the risk of major vascular events such as death.

The purpose of this evidence-based review of the ADVANCE trial is to determine if the results are clinically significant to health care professionals treating type 2 diabetic patients.

Student Reviewer's Conclusion:

The ADVANCE trial was a double-blind, placebo controlled trial. It was designed to evaluate if a combination anti-hypersensitive regimen of perindopril and indapamide is beneficial for all type 2 diabetic patients, regardless of their initial blood-pressure values. Previous trials have demonstrated that both thiazide diuretics and angiotensin-converting enzyme inhibitors have established benefits of both in reducing CVD and stroke incidence in patients with diabetes. Additionally, ACEI- or ARB-based treatments favorably affect the progression of diabetic nephropathy and reduce albuminuria. The ADVANCE trial examined a large study population for an extended study period. Concomitant therapy was also allowed in these patients, at the discretion of the physician. This creates a confounding factor of whether benefit is actually due to the active treatment or the concomitant therapy. However, this trial mirrors a "real-world" situation, in that most diabetic patients in the "real-world" setting are likely to be on multiple background therapies. Additionally, the primary and secondary endpoints were composite endpoints that used subjective measures to represent "worsening nephropathy" such as doubling of serum creatinine to a level of at least 200 Mmol/L. Subjective measures are likely to create bias. It was also uncertain how patient adherence and persistence to treatment was evaluated because this information was not stated. Results showed wide confidence intervals allowing one to question whether the effects were clinically meaningful. For example, the primary outcome showed a decrease in microvascular & macrovascular events (15.5% vs. 16.8% placebo, hazard ratio 0.91, 95% CI 0.83-1.00, p=0.04).

ADVANCE trial results are important because they highlight the concept that anti-hypertensives may be helpful in diabetes without routine monitoring of blood pressure. Infrequent monitoring represents a real-world setting, where time is limited and intensive blood pressure monitoring is impractical. Despite the large study numbers (n=11140) and extended duration (n=4.3 years), threats to validity make it impossible to conclude efficacy for this combination of drugs in achieving the reported outcomes. It is uncertain from this trial whether combination anti-hypertensive agents are beneficial for the outcomes evaluated. Additional studies with increased measures to increase internal validity should be performed to confirm these results so that they can applied externally.

Student Reviewer's Overall Grade: B—U = Possible to Uncertain usefulness.

Guest Editors' Opinion & Comments: Overall Grade: U = Uncertain validity and clinical usefulness.

What is this study really about, anyway? Is this study attempting to demonstrate that a combination of perindopril + indapamide is more efficacious than placebo

in reducing risks for vascular outcomes? This study is designed in such a way that this question cannot be answered due to the confusing problem of the concomitant medication usage. Therefore, we don't know the "cause" of the lowered blood pressure or the reduction in events.

Sometimes it is useful to take an indirect approach to a study and not be led by the authors, but rather be guided by the study design. Physicians had the option to change medications in an open-label way with the end result that patients got many medications that can lower blood pressure, and some patients in the comparison group even received the intervention under study. Therefore, this truly isn't a comparison of perindopril + indapamide versus placebo, but rather is a study of one group of patients receiving an unknown non-standardized assortment of physician-selected drugs compared to another group of patients

Element	Criteria	Comments/Threat
Study Design Assessment	Is the design appropriate to the research question? Is the research question useful? • For **efficacy,** use of **experimental study design** (meaning there was no choice made to determine intervention) • **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	Threat: Primary endpoint was changed while the study was being conducted to include both microvascular and macrovascular events jointly and separately and F/U was extended. **Changing major endpoints while study is being conducted creates the potential for bias.** Threat: Response to primary outcome effect was not clearly defined. Threat: Information on adherence to treatment was reported as "monitored," but was evaluated by patient recall.
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	Treatment was allocated by computer generated randomization codes A central randomization service was used, which should achieve concealing allocation of the randomization sequence.
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	
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: Difference between groups due to background concomitant therapy selection, used by discretion of examining physician. Threat: Composite endpoints with subjective components may result in greater potential for bias. Defining neuropathy as doubling of serum creatinine is not ideal. Glomerular filtration rate (GFR) and proteinuria are standard measurements used for this. *continued*

receiving an unknown non-standardized assortment of physician-selected drugs.

The editorialist, Kaplan, raises the interesting observation that it seems strange that blood pressure was not as well-controlled in the placebo group, given the availability of effective drugs and the patients' access to them. Since this does not seem like a chance effect given the small p-values, what would explain this? It is possible that the deck was stacked against the placebo group from the outset, given that they had what may have been less effective medication or care processes at the start. These patients would, therefore, have a greater exposure to risk and

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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: 73% patients adherent to active treatment, 74% adherent to placebo.
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: Authors estimated primary and secondary outcomes using Cox proportional hazard models without providing details of assumptions used in the models. Methods of censoring also raise questions. Assessing outcomes through models has been reported to potentially erroneously misrepresent outcomes by a relative difference of 50% or higher. Lachin PubMed ID # 11018568.
Usefulness Assessment	• **Clinically significant area + sufficient benefit size =** meaningful clinical benefit (consider efficacy vs effectiveness)	Threat: Confidence intervals are wide and their upper limits may not be clinically useful. Consequently, even if the study were valid, results can be considered inconclusive.
External Validity	How likely are research results to be realized in the real world considering population and circumstances for care? • Review n, inclusions, exclusions, baseline characteristics and intervention methods this is a **judgment call.**	Threat: Due to the wide confidence intervals, it is difficult to ascertain if the results are clinically meaningful. It is therefore difficult to apply these results to the population at large
Patient Perspective	• Consider benefits, harms, risks, costs, uncertainties, alternatives, applicability to which patients, adherence issues, potential for abuse, dependency issues and patient satisfaction	See Student Reviewer's Conclusions.
Provider Perspective	• Satisfaction, acceptability, likely appropriate application and actionability (e.g., FDA approval, affordability, external relevance, circumstances of care, able to apply, tools available)	These drugs are not FDA approved for diabetic patients or to prevent diabetic-associated events. They are also not widely used in the US. With threats to internal validity, it is uncertain whether the drugs are causal in reducing macrovascular/ microvascular events. The applicability of this combination of drugs for all diabetic patients is uncertain and therefore should not be used based on the results of this study. Due to threats to validity, there is insufficient information to prescribe this combination of drugs to all diabetic patients.

**Chart taken from the Delfini Group,LLC. Short Critical Appraisal Checklist: Updated 02/19/08. Use of this tool implies agreement to the legal terms and conditions at www.delfini.org.*

for longer because of higher blood pressure at the outset, and then would have to try and "catch-up" to the "intervention" group. If a patient starts out taking a pill that is believed to control blood pressure but for which there is no active ingredient, the best one can count on is some placebo effect. This would result in a time lag before discerning a need for greater control. There is evidence that even small changes in blood pressure outcomes can affect clinical outcomes.

Blood pressure is a surrogate marker. As such, in a study designed to look at an intervention which lowers blood pressure and results in a beneficial clinical outcome, the question is was it the lowered blood pressure that is responsible for the outcomes or was it something unique about the intervention?

Overall, to us, this study raises questions and answers none. It perhaps lends some support to the argument that lowering blood pressure (a surrogate marker) does indeed impact important clinical outcomes. This is highlighted by a mélange of drugs being used and so, making it unlikely that it is due to anything special or unique about any agent. But even with that, there are many flaws in this study that render such a conclusion uncertain.

About the Authors

Michael E. Stuart MD and Sheri A. Strite of Delfini Group combine decades of academic and practical experience in health care, clinical quality health systems improvements, research, training and leadership. To learn more, visit www.delfini,.org.

Sapna N. Patel is a 2010 Pharm. D. Candidate at the USC School of Pharmacy.

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4. Micromedex Drugdex Evaluations-Indapamide, copyright 2006 by Thomson MICROMEDEX.

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