NAVIGATOR Study

By Ashlee Klevens, 2013 PharmD Candidate; Michael E. Stuart, MD; and Sheri A. Strite

Introduction:

The NAVIGATOR study is a multinational, randomized, prospective, double-blinded, placebo controlled, 2 x 2 factorial trial.This study investigated whether treatment with Nateglinide or Valsatan would reduce progression to diabetes and new cardiovascular events in subjects with impaired glucose tolerance whom have established cardiovascular disease (CVD) or are at high risk for developing cardiovascular disease.

The 9,518 patients in this trial were randomly assigned to receive either: Natglinide with Valsartan,Nateglinide with Valsartan –placebo, Nateglinide-placebo with Valsartan or Valsartan-placebo with Nateglinide- placebo, as well as receive telephone- based lifestyle interventions aimed at reducing weight and dietary fat intake and increasing physical exercise.

The primary objectives of the NAVIGATOR study were to assess the effect of Nateglinide, and to evaluate the occurrence of three co- primary outcomes of the development of diabetes, a cardiovascular outcome (nonfatal MI, nonfatal stroke), or an extended cardiovascular outcome that was a composite of the core cardiovascular outcome (unstable angina).

Among persons with impaired glucose tolerance and either carvascular disease or risk factors for cardiovascular disease, Nateglinide did not reduce the incidence of diabetes or co primary composite cardiovascular outcomes.

Overall Grade: BU

About the Author

Ashlee Klevens is a Level 4 Student at the USC School 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."

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	No threat. The study design is appropriate for the research question proposed.
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	Minor threat. Although the participants were randomly assigned study arms based on an interactive voice- response telephone system, the study lacks information in concealing the control versus study group. Also, according to Table 1, there is an increase chance that the Placebo participants were more likely to have microalbuminuria, peripheral arterial stenosis, and have a higher GFR prior to receiving treatment, which may have an effect on outcomes.
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	Baseline characteristics differ in terms number of patients with diabetes, current smoking, prior MI, prior PCI, and prior history of statin use. During the preliminary randomization, when patients were started at a lower dose of the respective statin, the concealment of allocation was achieved via an interactive voice system. However, the generation of the randomization sequence was not mentioned. During the second phase of the trial, when patients were instructed to take the maximum dose of the respective statin, the details regarding the concealment of allocation of the randomization sequence was not mentioned.
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. The study was reported to be a double blinded, randomized clinical trial that evaluates patients in a 2 x 2 factorial design.There was no information detailing the methods of initially blinding the staff, nor how blinding methods were concealed throughout the study. Both of these examples may lead to a bias in how treatment was executed differently in both groups. Moreover, there lacks information regarding the subjects adherence to the medication, cross- over threats, and protocol deviations.

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. According toFigure 1, the study enrolled 43,502 participants in the study prior to randomization. 9306 were included in the randomization. In total, 7476 completed the trial. Therefore, there is attrition in the study design. There was greater than twenty percent dropout rate in the final analysis which may lead to a bias in final outcomes.
Assessment Bias	Assessors are blinded	Threat. The study consists of an Intention-to-treat analysis. Assessors were presumed to be blinded, but the study does not outline how blinding was maintained throughout the study.
	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	
Usefulness Assessment	Clinically significant area + sufficient benefit size = meaningful clinical benefit (consider efficacy vs effectiveness)	Threat. P-values for all outcomes were statistically insignificant.
External Validity	How likely are research results to be realized in the real world considering population and circumstances for care?	Minor threat. According to the American Heart Association, heart disease and stroke are the number one causes of death and disability among people with type 2 diabetes. In fact, at least 65 percent of people with diabetes die from some form of heart disease or stroke. With this said,studies such as the NAVIGATOR trial are extremely essential in determining and formulating new guidelines for disease management. However, the exclusion criteria amongst the participants in the NAVIGATOR trial withdrew a significant portion of the typical elderly patient using Nateglinide and/or Valsartan. For example, patients taking an ACE inhibitor prior to the study were excluded from the trial. For this reason, this article's external validity poses minor threat.
	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	Minor threat. This study aimed to identify if patients at risk of cardiovascular events were affected or reduced while using Nateglinide and Valsartan. Although the outcomes of this trial will affect the benefits and risks of patients using this medication, it is important that patients take into consideration the qualifications to participate in this study. For example, exclusion criteria (see Study Participants), the study medication, and the lifestyle modifications that took place during this trial.
Provider Perspective	Satisfaction, acceptability, likely appropriate application and actionability (e.g., FDA approval, affordability, external relevance, circumstances of care, able to apply, tools available)	No threat. Rather then assessing the benefits and risks of diabetes medications, NAVIGATOR study analyzed high- risk cardiovascular patients using Nateglinide (and Valsartan), and sought to measure the potential reduction of incidence or delay progression of cardiovascular outcomes.

*Chart taken from the DelfiniGroup,LLC. Short Critical Appraisal Checklist: Updated 02/19/08
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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