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EVIDENCE-BASED MEDICINE REVIEW

Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients

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INTRODUCTION
HPS2-THRIVE, a randomized, double-blind, multicenter study, studied the efficacy and safety of extended-release niacin in combination with laropiprant versus matching placebo in treating patients with a history of cardiovascular disease. The study included a total of 25,673 patients, who had a history of MI, cerebrovascular disease, peripheral artery disease, or diabetes with evidence of symptomatic coronary disease for a median follow-up period of 3.9 years. Patients underwent a process to standardize cholesterol-lowering therapy using simvastatin 40mg or simvastatin 40mg + ezetimibe 10mg before undergoing randomization. The study arm (N=12,838) received 2g of extended-release niacin + 40mg laropiprant in addition to standardized cholesterol-lowering therapy, while the comparator arm (N=12,835) received a matching placebo with the standardized cholesterol-lowering therapy. The primary outcome studied was a composite of non-fatal MI, death from coronary causes, stroke, and arterial revascularization, while the secondary outcomes were components of the primary outcomes and adverse drug reactions.

I. Trial Validity

Start of Trial	
Randomization/Concealment	• A total of 25,673 participants were randomized into the study, with 12,838 participants in the treatment arm with niacin ER/laropiprant + simvastatin 40mg with or without ezetimibe 10mg and 12,835 participants placebo arm with only simvastatin 40mg with or without ezetimibe 10mg. • In a pre-randomization run-in phase, the participants were given simvastatin 40mg daily, and if the dose was not as effective as their prior treatment or if their total cholesterol level was greater than 135 mg/dL after 4 weeks, ezetimibe 10mg daily was added. • The study used a minimized randomization program on the clinic IT system that helps maximize balance between the treatment groups with respect to prognostically important variables such as age, gender, history of prior disease, smoking status, lipid levels, blood pressure, ethnic origin, and history of prior statin use. • The study concealment was carried out via using a minimized randomization program on the clinic IT system.
Baseline Characteristics	• The baseline characteristics according to the participants' age, gender, ethnicity, prior cardiovascular disease history, LDL-C, and HDL-C levels were not statistically significantly different. The baseline characteristics are clinically similar between the study arm and the comparator arm. • The study consisted of patients with mean age of 65 years old, majority (83%) of male gender, of European or Chinese descent, with mean LDL-C level of 63 mg/dL and mean HDL-C level of 44 mg/dL.

During Trial	
Blinding	• The patients, clinicians, investigators, data collectors, and analysts were blinded to the treatment. • Laropiprant is a prostaglandin D2 receptor antagonist that has been shown in previous studies to improve adherence to niacin therapy by reducing flushing in up to two-thirds of patients. But flushing still occurs in a third of those patients who take laropiprant with niacin, which may have introduced bias into the study by suggesting to the patients and clinicians the groups to which they were assigned.
Equal Treatment	• The study had somewhat equal treatment of both study arms. • The study protocol allowed for "early recall visits," which were visits outside of the standard monitoring schedule if patients had severe symptoms thought to be related to study treatment. Since there was a significantly higher rate of adverse effects associated with the study treatment as compared to placebo with, for example, a 1.4% ($p<0.001$) higher incidence of infection and a 3.7% ($p<0.001$) higher incidence of disturbed diabetes control, this will have prompted greater healthcare exposure in terms of assessment visits in the experimental arm of the study. The greater frequency of follow-up visits by the treatment arm may have led to unequal treatment by prompting the subjects to receive better care and/or more motivation to pursue lifestyle improvements. Because the study protocol allowed for patients' lipid-lowering therapy to be altered and the study treatment discontinued by their physicians if their cholesterol was deemed inadequately controlled, possibly leading to inaccurate study dropout rates and better lipid-lowering results in the study arm. The study did not disclose how many of the 25% dropouts in the experimental group were switched from study medication to non-study statin due to inadequate treatment, but interference outside of the study investigators may have led to unequal treatment. • Non-study niacin use was minimal. Three participants from the experimental group and 9 from the placebo group were reported as taking non-study niacin. These participants account for less than 0.1% of each study arm, and are unlikely to influence the results of the study.
End of Trial	
Completeness of Outcome Data	• A total of 12,838 and 12,835 par-ticipants were analyzed in the treatment arm and placebo arm, respectively. • An equally small percentage of patients was lost to follow-up in both study arms (108 [0.8%] vs. 95 [0.7%] in treatment vs. place-bo). • The absolute risk difference (ARD) for the primary outcome is as follows: Any major vascular event: 0.005 [0.5%]. • The ARD for the safety outcomes is as follows: GI: 0.01 [1%], myo-pathy: 0.007 [0.7%], infection: 0.01 [1%], new onset DM: 0.01 [1%], and disturbed DM: 0.04 [4%]. • The percentage of patients lost to follow-up were greater than the absolute risk differences of the composite primary outcomes, signifying that the size of the missing data was large enough to possibly bias the study results.
Method of Outcome Analysis	• The authors of the study reported use of an intention-to-treat (ITT) analysis. ITT was verified by checking the figures and tables of the study. Thus, the number randomized was the same as the number analyzed. • Fasting blood lipid levels were collected for all participants at baseline. Central laboratory assays of "non-fasting" blood lipid levels of LDL-C and HDL-C were performed at baseline, at median follow-up of one year, and at the final visit in all participants, and annually for 5% of the total participants. Use of non-fasting blood lipid levels may have added erroneous reporting of true lipid levels.

II. Trial Results

The primary outcome was a composite consisting of nonfatal MI, death from coronary causes, stroke, and revascularization events. The rate of each individual event subtype was reported in the study, and generally showed nonsignificant trends toward better results with niacin ER/laropiprant. The composite result suggests a statistically as well as clinically non-significant reduction in any major vascular event.

Primary and Secondary Outcomes	[Niacin-Laropiprant Dose] N=12,838	[Placebo] N=12835	Relative Risk (RR)	Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	Number Needed to Treat (NNT) or Number Needed to Harm (NNH)	P-value
Any major vascular event	1696 (13.2%)	1758 (13.7%)	0.96 (0.90-1.03)	4%	0.5%	N/A	0.29
Major Coronary Event	668 (5.2%)	694 (5.4%)	0.96 (0.87-1.07)	4%	0.2%	N/A	0.51
Stroke	498 (3.9%)	499 (3.9%)	1.00 (0.88-1.13)	0%	0.009%	N/A	0.56
Revascularization	807 (6.3%)	897 (7%)	0.9 (0.82-0.99)	10%	0.7%	142	0.03

Safety Outcomes	[Niacin-Laropiprant Dose] N=12,838	[Placebo] N=12835	Relative Risk (RR)	Relative Risk Increase (RRI)	Absolute Risk Increase (ARI)	Number Needed to Treat (NNT) or Number Needed to Harm (NNH)	P-value
GI ADE	620 (4.8%)	491 (3.8%)	1.26	26%	1%	100	<0.001
Musculoskeletal ADE	481 (3.7%)	385 (3.0%)	1.25	25%	-0.7%	134	<0.001
Infection ADE	1031 (8.0%)	853 (6.6%)	1.21	21%	1%	72	<0.001
New Onset DM	494/8704 (5.7%)	376/8670 (4.3%)	1.31	31%	1%	75	<0.001
Disturbed DM Control	460/4134 (11.1%)	311/4165 (7.5%)	1.49	49%	4%	27	<0.001

III. Trial Applicability

Patient Applicability	• The results of this study apply to patients who are 50 to 80 years old and have a history of myocardial infarction, cerebrovascular atherosclerotic disease, peripheral artery disease, or diabetes mellitus with symptomatic coronary heart disease. • The study is applicable to patients with similar baseline characteristics as the study participants, with a mean age of 65 years old, mostly (83%) of male gender, of European or Chinese descent, with mean LDL-C level of 63 mg/dL and mean HDL-C level of 44 mg/dL. • Some key exclusion criteria are severe renal insufficiency with creatinine >2.3 mg/dL, history of chronic liver disease or abnormal liver function tests (i.e. ALT > 1.5x ULN), and recent acute MI, coronary syndrome, or stroke within 3 months of screening.
Intervention Applicability	• The study used a combination of niacin/laropiprant with simvastatin or simvastatin plus ezetimibe in a patient population with established CVD. Niacin is commonly and easily accessible and obtainable for patients over-the-counter, but currently the combination product of niacin ER/laropiprant is not available in the US market.
Patient-Important Outcomes Measured	The outcomes measured in the study were: 1. Clinical endpoints directly measuring cardiovascular event rates in treated patients. 2. Blood lipid levels measured as a surrogate endpoint. The study included clinically mean-ingful primary outcomes for pa-tients with cardiovascular disease. • Although the study drug result-ed in an average decrease of 10 mg/dL of LDL-C level and an average increase of 6 mg/dL of HDL-C level, the clinical end-point was not reflective of the expected benefit of the changes in lipid level. • The measure of outcomes re-garding actual cardiovascular events is clinically more mean-ingful regardless of significant changes in surrogate endpoints.
Balance of Benefits vs. Harms	• Taking niacin ER/laropiprant on top of moderate-intensity statin-based treatment did not significantly reduce the risk of heart attacks [absolute risk reduction; ARR 0.2%], strokes [ARR 0.009%], and revascularization rates [ARR 0.7%]. • Taking niacin ER/laropiprant led to a variety of serious adverse drug reactions (ADRs). Many of the ADRs in the trial were known before the study, such as skin and gastrointestinal disorders, but some were discovered during the study, such as an increased risk of infection. • Although general, measurable changes were observed in LDL-lowering and HDL-elevating effects of niacin ER/laropiprant, they did not result in a statistically significant reduction of cardiovascular event risk. • Primary outcome was non-significantly reduced in the niacin ER/laropiprant group with an absolute risk reduction of 0.5% (p=0.29). The number needed to treat was 206, but given the non-significant p-value, the actual number may be much greater. Conversely, overall mortality was significantly increased in the niacin ER/laropiprant group with a number necessary to harm of 205. Niacin ER/laropiprant treatment was also associated with significantly higher rates of known adverse events of niacin, such as GI, musculoskeletal, skin, bleeding events, and decreased glycemic control, in addition to an unknown adverse event of niacin, namely, infectious adverse events. • Overall, the benefits do not outweigh the potential risks of the study drug.

Conclusion for Healthcare Professionals

HPS2-THRIVE demonstrated that niacin ER/ laropiprant versus placebo with simvastatin 40mg and/or ezetimibe 10mg did not produce statistically significant benefits in decreasing the risk of major vascular events while leading to a number of clinically significant serious adverse events. The study was well designed overall with a large and diverse study population. The flushing associated with niacin may have introduced bias into the study by suggesting to the patients and the clinicians the groups to which they were assigned. In addition, the fact that over 33% of those who started the active niacin ER/laropiprant phase withdrew during the LDL cholesterol-standardization phase due to adverse events may have introduced additional bias in the study results by underestimating the magnitude of adverse events. Furthermore, the percentage of patients lost to follow-up were greater than the absolute risk differences of all three primary outcomes, signifying that the size of the missing data was large enough to possibly bias the study results. Overall, it can be concluded that the known harms outweigh the clinically non-significant benefits in the combination niacin ER/laropiprant treatment in addition to statin therapy in patients with atherosclerotic vascular disease with LDL-C and HDL-C levels already at goal range.

Conclusion for Patients

HPS2-THRIVE showed that niacin ER/laropiprant with simvastatin and or ezetimibe did not produce significant benefits in decreasing the risk of heart attack and stroke, but it did lead to a number of significant serious side effects. The study was well-designed overall with a large and diverse study population. The current standard of therapy for lowering cholesterol in high-risk patients is high-intensity statins, unless not tolerated. Although the background cholesterol-lowering therapy is not representative of current standard of care, it can still be safely concluded that niacin ER/laropiprant should not be recommended as an add-on therapy. Overall, it can be concluded that there is more harm than potential benefit when taking the combination niacin ER/laropiprant treatment in addition to statin therapy in patients with atherosclerotic vascular disease with LDL-C and HDL-C levels already at goal range.

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