Researchers present highly anticipated IMPROVE-IT results

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More than a decade ago, researchers from Brigham and Women's Hospital (BWH) demonstrated that a high dose statin, which lowered cholesterol further than a regular dose statin, provided better clinical outcomes. But questions remained about whether further reducing cholesterol would be even more effective in reducing cardiovascular-related events.

Now, results of the highly anticipated IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), co-led by researchers at BWH and Duke Medicine, indicate that adding a second drug, ezetimibe, that blocks cholesterol absorption, resulted in a significant 6.4 percent reduction in the number of cardiovascular events.

The findings, presented as a late breaking clinical trial at the American Heart Association Scientific Sessions on Nov. 17, 2014, clarify a long-standing question in cardiac care about whether reducing cholesterol to even lower levels might improve outcomes. Complete publication of the data is expected in the coming months.

"There is a lot of evidence that demonstrates that low cholesterol is better, and our findings suggest that even lower is even better," said Christopher Cannon, MD, principal investigator of IMPROVE-IT and a cardiologist and researcher in the TIMI Study Group at BWH. "More broadly, the results of IMPROVE- IT re-emphasize the central role of lowering LDL cholesterol for the treatment of high risk patients."

In this multicenter, double-blind, placebo-controlled international randomized trial, researchers enrolled 18,144 patients with acute coronary syndrome (ACS), described as heart attacks or worsening chest pain, and all were treated according to the previously existing guidelines with a statin (simvastatin).

In the control group, patients who received statin therapy alone reached a median LDL cholesterol level of 69 mg/dl for a median of six years. Researchers found that when patients received the non-statin medication ezetimibe, in addition to the statin (ezetimibe/simvastatin combination/brand name VYTORIN), LDL cholesterol was reduced 20 percent further to a median level of 54 mg/dl, and this led to a statistically significant 6.4 percent reduction in the number of cardiovascular events. (p=0.016) After seven years, the combined rate of cardiac death, heart attack, stroke, hospitalization for worsening chest pain, or need for revascularization, was reduced from 34.7 percent in the control group to 32.7 percent in the group that received the combination therapy. Additionally, researchers report that approximately two cardiovascular events were prevented in the trial for every 100 patients treated, with the difference driven by reductions in heart attack or stroke.

"This trial demonstrates the importance of careful measurement of long-term outcomes in randomized trials for medicines that are taken for chronic diseases," said Robert Califf, MD, vice chancellor for clinical research at Duke and co-study chair of the trial. "We were looking for a small effect and we found an effect very close to what we expected, clearly favoring the group taking ezetimibe/simvastatin. The trial confirmed the existing safety profile of ezetimibe."

"Our findings suggest that, among this population of ACS patients, we may want to consider changes to our clinical guidelines, which might include an LDL cholesterol target of closer to 55, or lower," said Eugene

Braunwald, MD, co-study chair, and founding chairman of the TIMI Study Group at BWH.

Additional data from the trial will be presented at the AHA meeting on Tuesday in a trial update session. The presentation, the first additional analysis of the study database led by the Duke Clinical Research Institute, will focus on the population of individuals who completed the study on medication.

"We are using this analysis as a first look at the findings of the primary analysis, and to look at the data among patients only during the time that they actually remained on treatment during the study," said Michael Blazing, MD, associate professor of medicine and director of outpatient services at the Duke Heart Center who will present the findings of the on-treatment group in the Tuesday session.

Ezetimibe is a drug approved to lower plasma cholesterol levels by decreasing absorption of LDL cholesterol in the small intestine, and is additive to the role that statins play in lowering cholesterol. Ezetimibe and the ezetimibe/simvastatin are sold by Merck, which sponsored and provided funding for this study.

Provided by Brigham and Women's Hospital