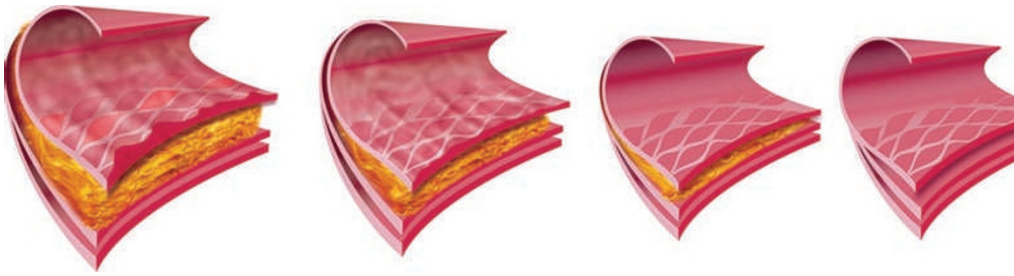
CORONARY ARTERY DISEASE

Niacin combined with statin treatment reduces carotid intima-media thickness in patients at risk of heart disease



According to recent evidence from the ARBITER 6-HALTS trial, treatment with extended-release niacin, in combination with statin therapy, significantly increases HDL-cholesterol levels and causes a small, but significant, reduction in carotid intima-media thickness (cIMT) in comparison with treatment with statin therapy and ezetimibe in patients at risk of heart disease.

Clinical approaches to regulate circulating cholesterol levels have benefited from the widespread use of statins—patients receiving statin therapy have a 16% reduction in the risk for coronary death or any major cardiovascular event compared with individuals on other standard-dose therapies. However, despite the significant benefits of statins, residual cardiovascular risk has been reported with statin monotherapy, meaning alternative approaches, including increasing HDL-cholesterol levels, are receiving increased interest.

"Given the very strong epidemiologic link [between] levels of HDL cholesterol and cardiovascular events and mortality, the promise of raising HDL for cardiovascular prevention has been one of the most hoped for and anticipated approaches in medicine ... however, we have not had the breakthrough large clinical trials showing benefit of this approach in the current era of aggressive LDL lowering" says Christopher Cannon, Senior Investigator of the TIMI Study Group at Brigham and Women's Hospital and Associate Professor of Medicine at Harvard Medical School, USA.

Allen Taylor and colleagues randomly assigned 208 patients (mean age 65±11 years) with known coronary heart disease, or coronary heart disease risk equivalent, all of whom were on statin monotherapy, to receive co-treatment with either niacin or ezetimibe. Before receiving treatment with the secondary agent, all patients were confirmed to have LDL-cholesterol levels <2.6 mmol/l as well as HDL-cholesterol levels <1.3 mmol/l for men (n = 167) and <1.4 mmol/l for women (n = 41). The primary end point for the study was the difference in the reduction from baseline in the mean cIMT between treatment groups after 14 months. This surrogate measure of improvement in atherosclerosis has been surrounded by much heated debate in recent times. Secondary end points included changes in lipid values and major cardiovascular events.

The efficacy of niacin in changing mean cIMT at 8 and 14 months follow-up was significantly greater than that of ezetimibe. Specifically, niacin therapy significantly reduced mean and maximal cIMT by up to ~0.014 mm and ~0.018 mm, respectively, while ezetimibe failed to cause any significant change. With respect to secondary end points, patients receiving niacin had significantly increased HDL-cholesterol levels in comparison with levels in patients on ezetimibe treatment. In addition, both treatment groups had lower levels of LDL cholesterol and triglycerides, although the greatest reduction in LDL-cholesterol values was following ezetimibe treatment. The authors also noted the lowest incidence of major adverse cardiovascular events in patients receiving niacin.

Following *post hoc* data analysis, the investigators found that LDL-cholesterol levels in patients from the ezetimibe treatment group, but not the niacin treatment group, were significantly inversely correlated to mean cIMT. This correlation implies that ezetimibe-induced reduction of LDL cholesterol is associated with increased cIMT. The investigators speculate that this paradoxical effect, which is in disagreement with results from the SANDS trial, may be due to the reported inhibition of the high-affinity HDL receptor B1 by ezetimibe, thus leading to a disruption of reverse cholesterol transport. Crucially, these results, and in particular the adverse effects of ezetimibe treatment, question the use of LDL-cholesterol reduction as a reliable indicator of the clinical efficacy of drugs used to prevent atherosclerosis.

These findings imply that to complement statin therapy in patients at risk of major cardiovascular events, increasing HDL-cholesterol levels through niacin treatment is superior to ezetimibe-induced reduction in LDL-cholesterol levels. However, this trial has been surrounded by much discussion in the cardiology community, with many clinicians strongly believing that clinical decisions should not be made on the basis of surrogate end points such as cIMT. "What we now look forward to are large clinical outcome studies that can help define the tolerability and, importantly, the safety of adding high-dose niacin in patients getting aggressive statin therapy, and the actual efficacy on prevention of clinical events," concludes Cannon.

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