

CORRESPONDENCE



Niacin Compared with Ezetimibe

TO THE EDITOR: Taylor and colleagues (Nov. 26 issue)¹ find that the use of extended-release niacin causes a significant regression of carotid intima-media thickness when combined with a statin. We agree with Kastelein and Bots in the accompanying editorial² that the results of the ARBITER 6–HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies) trial do not clarify whether the beneficial effects of niacin are the result of the effects of the drug on high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, remnant particles, Lp(a) lipoprotein, or inflammation. However, we also wish to highlight the effect of niacin on blood pressure as a possible mechanism for the differences in carotid intima-media thickness found in the trial.

More than 85% of the patients in the trial were hypertensive. Niacin has been shown to be significant in lowering blood pressure in hypertensive patients, an effect that may be responsible for some of its cardiovascular benefits.³ In

contrast, ezetimibe is not known to have such pleiotropic effects.

This effect on blood pressure is particularly important when using common carotid intima-media thickness as an end point; previous studies have suggested that blood pressure has a greater influence on this measure than LDL cholesterol, particularly when cholesterol levels are low.^{4,5} Did Taylor and colleagues note any difference in blood pressure between the two treatment groups at the end of the trial?

Alistair C. Lindsay, M.R.C.P.

University of Oxford
Oxford, United Kingdom
alistair.lindsay@btinternet.com

Julian P. Halcox, F.R.C.P.

University of Cardiff
Cardiff, United Kingdom

Drs. Lindsay and Halcox report receiving consulting and speaking fees from Merck. No other potential conflict of interest relevant to this letter was reported.

1. Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med* 2009;361:2113-22.
2. Kastelein JJP, Bots ML. Statin therapy with ezetimibe or niacin in high-risk patients. *N Engl J Med* 2009;361:2180-3.
3. Bays HE, Rader DJ. Does nicotinic acid (niacin) lower blood pressure? *Int J Clin Pract* 2009;63:151-9.
4. Polak JF, Person SD, Wei GS, et al. Segment-specific associations of carotid intima-media thickness with cardiovascular risk factors: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Stroke* 2010;41:9-15.
5. Zanchetti A, Bond MG, Hennig M, et al. Risk factors associated with alterations in carotid intima-media thickness in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis. *J Hypertens* 1998;16:949-61.

THIS WEEK'S LETTERS

- 1046 Niacin Compared with Ezetimibe
- 1048 Platelet Inhibition with Cangrelor
- 1050 Dabigatran versus Warfarin for Venous Thromboembolism
- 1051 Hypothermia for Perinatal Asphyxial Encephalopathy
- 1052 Continuing Medical Education — Limiting Industry's Influence
- 1054 Clinical Trials That Explicitly Exclude Gay and Lesbian Patients

TO THE EDITOR: In the ARBITER 6–HALTS trial, the investigators reported an inverse relationship between the change in LDL cholesterol level and the change in carotid intima-media thickness in the ezetimibe group (Pearson's $r = -0.31$, $P < 0.001$), from which they hypothesized a harmful effect of ezetimibe. We assessed the same relationship

in the group treated with simvastatin plus ezetimibe in the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial.¹ We calculated the change in LDL cholesterol as the difference in LDL cholesterol levels at the end of the study and at screening. In contrast with the findings in the ARBITER 6–HALTS study, we found a positive Pearson's correlation coefficient for the changes in LDL cholesterol and carotid intima–media thickness (0.17, $P=0.004$). In fact, in a multivariate analysis, the change in LDL cholesterol remained a positive predictor for end-of-study carotid intima–media thickness ($P=0.04$), after correction for age, body-mass index, baseline carotid intima–media thickness, and the changes in levels of HDL cholesterol and triglycerides. In conclusion, in contrast with the findings in the ARBITER 6–HALTS trial, we found that in the group treated with simvastatin plus ezetimibe a greater reduction in levels of LDL cholesterol resulted in less progression of carotid intima–media thickness.

Raphaël Duivenvoorden, M.D.

Menno Vergeer, M.D.

John J.P. Kastelein, M.D., Ph.D.

Academic Medical Center
Amsterdam, the Netherlands
j.j.kastelein@amc.uva.nl

Dr. Kastelein reports receiving consulting fees, lecture fees, and grant support from Merck and lecture fees from Schering-Plough. No other potential conflict of interest relevant to this letter was reported.

1. Kastelein JJP, Akdim F, Stroes ESG, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;358:1431-43. [Erratum, *N Engl J Med* 2008;358:1977.]

TO THE EDITOR: To minimize bias, optimal clinical trial designs include patients on the basis of intention to treat. In contrast, the randomized, comparative-effectiveness trial by Taylor and colleagues included outcome results only on those patients who were still enrolled after 14 months. Among those initially enrolled, 40.9% of 176 patients in the ezetimibe group had diabetes mellitus and 39.0% of 187 patients in the niacin group had diabetes (see the Supplementary Appendix in the article by Taylor et al., available at NEJM.org). Among the patients remaining in the study at 14 months, 40% of those in the ezetimibe group had diabetes, whereas only 32% of those in the niacin group had diabetes. The drop in the proportion of patients with diabetes in the niacin group still enrolled at 14 months was predictable, since niacin

can impair glucose tolerance.^{1,2} Baseline glucose levels (means \pm SD) were 104.5 \pm 32.4 in the niacin group and 104.2 \pm 28.1 in the ezetimibe group at enrollment (Supplementary Appendix). Since these means are in the normal range, and since physiologic limits restrict the range of low outliers at those means, the large standard deviations suggest that there were outliers with high levels of glucose. The baseline glucose levels of those remaining in the study after 14 months were 100.1 \pm 18.9 in the niacin group and 104.0 \pm 27.8 in the ezetimibe group. Only in the niacin group was the standard deviation in baseline glucose level strikingly lower than in all who were initially enrolled in that group. This suggests that patients in the niacin group with more poorly controlled diabetes were more likely to drop out of the study than were those in the ezetimibe group. Since people with diabetes can have worse cardiovascular outcomes, the disparity between the two groups in the study reflects an important, a priori bias in study design. The two groups thus have substantially different risk profiles, which means that the results are probably biased because of selective dropout in the group treated with niacin among patients with poorly controlled diabetes.

Stanley H. Weiss, M.D.

University of Medicine and Dentistry of New Jersey—
New Jersey Medical School
Newark, NJ
weiss@umdnj.edu

No potential conflict of interest relevant to this letter was reported.

1. Pandit MK, Burke J, Gustafson AB, Minocha A, Peiris AN. Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993;118:529-39.

2. Garg A, Grundy SM. Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. *JAMA* 1990; 264:723-6.

TO THE EDITOR: Taylor and colleagues report a reduction in carotid intima–media thickness when niacin is added to long-term statin therapy, whereas carotid intima–media thickness increased when ezetimibe was added to long-term statin therapy. Although the reduction in wall thickness may be attributed to drug-related regression, it is important to confirm that the decrease in wall thickness is not primarily related to an increase in the vessel lumen, with no overall change in the vessel cross-sectional area, particularly given niacin's vasoactive properties. The authors should confirm that there were no in-treatment differences in blood pressure and, more important, provide

data regarding baseline and final lumen diameters in the two treatment groups.

Mary J. Roman, M.D.

Weill Cornell Medical College
New York, NY
mroman@med.cornell.edu

No potential conflict of interest relevant to this letter was reported.

THE AUTHORS REPLY: In the ARBITER 6–HALTS trial, systolic blood pressure in the ezetimibe group declined by 4 ± 2 mm Hg and that in the niacin group declined by 3 ± 2 mm Hg; diastolic blood pressure declined by 2 ± 1 mm Hg and 3 ± 1 mm Hg, respectively (P not significant for both comparisons). Thus, changes in blood pressure cannot account for our findings regarding carotid intima–media thickness.

We find it plausible that the investigators in the ENHANCE trial could not observe a similar paradoxical relationship between reduction in LDL cholesterol level and progression in carotid intima–media thickness, which is consistent with the overall null result of that placebo-controlled study of ezetimibe. The clinical relevance of the ENHANCE data to that of the ARBITER 6–HALTS trial is questionable, given the major differences in the two study populations, with participants in the ENHANCE trial being younger patients with heterozygous familial hypercholesterolemia, having a very low prevalence of cardiovascular disease, and having a much higher mean baseline and therapeutic levels of LDL cholesterol (140 to 190 mg per deciliter) and HDL cholesterol (51 mg per deciliter). The ARBITER 6–HALTS data convincingly show that ezetimibe can lead to paradoxical progression of atherosclerosis the greater the degree of reduction in LDL cholesterol levels. Our initial findings were unchanged in a subsequent analysis that included an updated data set of last-observation-carried-forward results among 315 patients and multivariable models controlling for other cardiovascular risk factors. Ezetimibe has multiple, theoretically adverse effects on sev-

eral key cholesterol transport receptors, and the clinical relevance of these effects should be further examined within relevant patient populations, such as that enrolled in the ARBITER 6–HALTS trial.

Niacin can induce generally small and time-limited changes in glycemic control. However, such changes do not account for our results. Baseline glycemic control was similar among patients with diabetes in both treatment groups, including those who completed the study and those who dropped out (median baseline glucose level, 107 and 115 mg per deciliter, respectively); however, the distributions were non-normal, which accounts for the different standard deviations. Baseline levels of blood glucose (P=0.54) and changes in level of blood glucose (P=0.74) were similar among patients who dropped out of the study, whether from the niacin or the ezetimibe group. Significant regression of carotid intima–media thickness was observed in patients with diabetes who were treated with niacin in a last-observation-carried-forward analysis, whereas no such effect was observed in such patients who were treated with ezetimibe, thereby eliminating concern over potential bias resulting from the differential drop-out of patients with poorly controlled diabetes.

Our analysis of carotid intima–media thickness did not include an assessment of lumen diameters because acoustic shadowing makes measurement of the near wall of the carotid artery prone to error. However, a change in carotid dimensions is unlikely given the similarity of changes in the blood pressure of both groups during the trial.

Allen J. Taylor, M.D.

Washington Hospital Center
Washington, DC
allen.taylor@medstar.net

Eric J. Stanek, Pharm.D.

Medco Health Solutions
Franklin Lakes, NJ

Since publication of their article, the authors report no further potential conflict of interest.

Platelet Inhibition with Cangrelor

TO THE EDITOR: Harrington et al.¹ and Bhatt et al.² (Dec. 10 issue) describe the results of studies of platelet inhibition with intravenous cangrelor in patients undergoing percutaneous coronary intervention (PCI). In the study by Harrington

et al., 996 patients with myocardial infarction with ST-segment elevation were enrolled. In this select group of patients, the administration of oral antiplatelet agents is not always an option. In our institution, such drugs could not be administered to