A Time to Stop Prescribing Antioxidant Vitamins to Prevent and Treat Heart Disease?

Lewis H. Kuller

The article by Cheung et al.1 “Antioxidant supplements block the response of HDL to simvastatin-niacin therapy in patients with coronary artery disease and low HDL” in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, demonstrates a possibly important and troubling observation. The addition of an antioxidant “cocktail,” comprising vitamins E and C, β-carotene, and selenium, for participants on simvastatin and niacin (SNA) therapy, resulted in a significant blunting of the apo A1 and HDL2 response compared with those on lipid-lowering drugs alone (SN). None of the HDL-related changes for the antioxidant group only were different from those for placebo.3 There are still ongoing placebo-controlled clinical trials of antioxidant cocktails including vitamin E. These trials are mainly in primary prevention and in lower-risk populations.4–6

If we assume that the results of the study of Cheung et al7 are not random variations, then what may account for the blunting of the HDL2 and apoA1 effect? There were 4 agents in the antioxidant cocktail, and we have no way of determining which 1 or ones are the culprit or whether it is the antioxidants overall that have an adverse effect. Vitamin E apparently increases cholesteryl ester transfer protein activity7 and decreases HDL cholesterol. Vitamin E is transported by lipoproteins.8 Does the binding of vitamin E to HDL cholesterol reduce the transport of cholesterol from the arterial wall to nascent HDL and thus, result in a shortening of the half-life of HDL in plasma? Do the antioxidants adversely affect the esterification of cholesterol by lecithin: cholesterol acyltransferase? The specific biochemical pharmacological effects will require detailed studies. It will be important to determine whether the blunting of the HDL effect is limited to a small subsample, especially those also taking lipid-lowering drugs, or whether it is found in most subjects. There also could be a genetic drug-drug interaction.

What do the results of the study mean for clinical practice? Given the lack of efficacy of antioxidants in clinical trials to date, antioxidant vitamin combinations above the recommended dietary allowances should not be recommended for prevention or treatment of cardiovascular disease. It will be important that physicians advise their patients that the use of antioxidants could be hazardous, especially in combination with lipid-lowering drugs. The next chapter in the antioxidant saga will depend, in part, on the results of ongoing clinical trials.4–6

References


From the Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pa. Correspondence to Lewis H. Kuller, MD, DrPH, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto St, Pittsburgh, PA 15261. (Arterioscler Thromb Vasc Biol. 2001;21:1253.) © 2001 American Heart Association, Inc. Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org

See page 1320

The unexplained results in a clinical trial are often chance findings, given the numerous possible analyses. The statistical test of significance is not meaningful in such an analysis because there was no prior hypothesis before the data were reviewed. It is probably better to provide a point estimate of the effect and the confidence limits. The unusual findings should not, however, be swept under the rug because they were not part of the planned analysis. The results should be presented so that other investigators can either substantiate or refute these observations with different data sets. The authors did not provide the results of the clinical trial for the primary end points. At the March 2001 American College of Cardiology meeting, the research group from Seattle (Zhao and colleagues2) presented preliminary results of the trial that showed that the combination of antioxidants and lipid-lowering drugs (SNA) not only blunted the HDL response but also had substantial adverse effects with regard to the primary end points of changes in coronary artery disease based on angiography. The SNA group had a 7% increase compared with a 4% decrease in the SN-only group with regard to measures of coronary stenosis, and the antioxidant group alone had a 15% increase compared with a 34% increase for the placebo group.

The initial enthusiasm for antioxidant therapy to prevent or treat cardiovascular disease has been substantially tempered by a series of negative clinical trials for both vitamins E and C and β-carotene.3 Most of the vitamin E results have been in secondary prevention trials, whereas β-carotene has not been efficacious even in primary prevention. The only recent trial to show a possible benefit of vitamin E was for secondary prevention in patients with end-stage renal disease. The Alpha Tocopherol Beta Carotene Cancer Prevention Trial reported an increase in cerebral hemorrhage for patients who were taking 50 mg of vitamin E daily compared with placebo.3
A Time to Stop Prescribing Antioxidant Vitamins to Prevent and Treat Heart Disease?

Lewis H. Kuller

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/21/8/1253

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/