Effect of Ramipril and Vitamin E on Atherosclerosis

To the Editor:

In their study, Lonn et al. report on the results of the SECURE study, which evaluated the effect of ramipril and vitamin E on atherosclerosis. The authors conclude that long-term treatment with ramipril has a beneficial effect on atherosclerosis progression whereas vitamin E has no effect.

The authors use the term “atherosclerosis progression” in the title and throughout the text. However, the study outcomes were the progression slope of carotid intimal medial thickness (IMT). IMT evaluated by B-mode ultrasound has been proposed as an additional independent risk factor for cardiovascular disease because it has been associated with an increased risk of myocardial infarction and stroke. Nevertheless, an increased IMT does not fit with the current pathological figure of atherosclerosis, from the fatty streak to the complicated plaque. The biochemical mechanisms that alter the IMT are still unknown. In contrast, the biochemical pathways of the atherosclerosis process are well known and supported by a huge number of experimental evidences based on cellular and animal models. In this context, the most studied mechanism is the oxidative modification of low density lipoprotein (LDL) and its metabolism in the arterial wall by the monocyte/macrophage-derived foam cells. Support for this concept has been given by studies with antioxidants, including vitamin E, which showed a reduction of experimental atherosclerosis. Vitamin E also reduces the uptake of oxidized LDL by foam cells of atherosclerotic plaque in vivo in humans. According to these considerations, the lack of effect of vitamin E in reducing the progression slope of IMT is not surprising. In fact, to the best of our knowledge, there are no data that correlate oxidant stress with an increased IMT. The use of the term “progression slope of IMT” as synonymous with “atherosclerosis progression” is not correct and could confuse interpretation of the study, especially in reference to vitamin E, which is supposed to act as an antioxidant. On the other hand, the beneficial effect of ramipril in reducing IMT increase is important and could give new insight into the physiopathology of IMT modifications and the role of the angiotensin-converting enzyme (ACE) system in this context. In conclusion, the lack of effect of vitamin E in this study means that vitamin E or antioxidants are not effective on the progression slope of IMT. Thus, the authors should not conclude that vitamin E had no effect on atherosclerosis progression.

L. Iuliano, MD
F. Micheletta, MD
F. Violi, MD

The Institute of Clinical Medicine
University La Sapienza
Rome, Italy

L.G. Spagnoli, MD
Department of Pathology
University Tor Vergata
Rome, Italy


Response

In the SECURE study, we found that long-term therapy with ramipril reduced the progression of carotid intima-media thickness (IMT) in high risk patients, whereas natural source Vitamin E had a neutral effect. We interpreted these findings to be indicative of a beneficial effect of ACE inhibition and of a neutral effect of Vitamin E on atherosclerosis progression. Iuliano et al. question the interpretation of the SECURE study results. Specifically, they suggest that carotid IMT and its changes are not reflective of atherosclerosis extent and progression.

In response, we point out that carotid IMT is a widely accepted surrogate marker used extensively in the detection and monitoring of the progression of subclinical atherosclerosis. Measurements of carotid IMT are based on direct imaging of the arterial wall and, therefore, present clear advantages over angiographic techniques. As reviewed by us and others, there are several lines of evidence that strongly support the use of carotid IMT as a valid surrogate for atherosclerosis. (Lonn. is a brief review that references publications supporting the validity of carotid IMT as a surrogate measure of arteriosclerosis.) Thus, ultrasound measurements of carotid IMT correlate well with measurements obtained by histology. A number of studies show moderate to good correlations with coronary angiography and, more recently, with coronary calcification by electron-beam computed tomography (EBCT) and with ischemia on stress testing. These studies indicate that carotid IMT can be used as a marker not only of site-specific atherosclerosis in the carotid circulation but also of generalized atherosclerosis, including disease in the coronary arteries. Many studies have reported good correlations with classical, as well as emerging, risk factors for atherosclerosis. Such correlations are present not only for hypertension, which may affect dominantly the arterial media, but also for cholesterol, diabetes, glycemia, and other risk factors directly involved in the genesis and progression of atherosclerotic lesions. Clinical trials, using lipid-lowering drugs, have repeatedly demonstrated decreased progression and even regression of carotid IMT, and the results of such trials are fully concordant with the results of statin trials on coronary angiographic measures of atherosclerosis and with results of large studies with clinical outcomes. Finally, data from prospective cohort studies, involving over 20,000 individuals, demonstrate that carotid IMT measurements obtained at a given point in time are independent predictors of myocardial infarction and stroke and the study by Hodis et al. indicates that changes in carotid IMT evaluated from serial examinations...
correlate with increased risk for coronary events. In fact, the use of carotid IMT in the assessment of effects of antioxidants on atherosclerosis was suggested by the strongest proponent of the antioxidant hypothesis of atherosclerosis, Dr Daniel Steinberg.

We realize that no surrogate measurement of atherosclerosis is perfect; nevertheless, in addition to the arguments presented above, the results of the SECURE trial are fully concordant with the results of the large parent HOPE trial, which showed a reduction in the risk of cardiovascular death and major vascular events with ramipril but a neutral effect with Vitamin E. Furthermore, other large trials with “hard” clinical endpoints have also generally failed to demonstrate benefits associated with Vitamin E in cardiovascular prevention.

We cannot fully exclude that Vitamin E may dominantly influence very early processes in atherogenesis, and that these very early changes may be difficult to detect by carotid IMT measures. Further research into use of antioxidants, including combinations of antioxidants, is warranted. Nevertheless, the failure of Vitamin E to result in improved clinical outcomes in HOPE and other large clinical trials raises major questions about the use of this agent in preventing atherosclerosis progression and its sequela.

For now, we need to focus on consistently and aggressively implementing proven preventive strategies, including smoking cessation, cholesterol and blood pressure lowering and, in high risk individuals targeted for secondary prevention, the use of drugs such as aspirin, statins, β-blockers, and ACE inhibitors.

Eva M. Lonn, MD, MSc
Salim Yusuf, MBBS, DPhil
Qilong Yi, PhD
Sandra Smith, RDMS
Anne Moore-Cox
Jackie Bosch, MSc
McMaster University
Department of Medicine
Hamilton, Ontario

Vladimir Dzavik, MD
The University of Alberta Hospitals
Edmonton, Alberta

C. Ian Doris, MBChB
McMaster University
Department of Radiology
Hamilton, Ontario

Ward A. Riley, PhD
Bowman Grey School of Medicine
Department of Neurology
Winston-Salem, North Carolina

Koon K. Teo, MB, PhD
The University of Alberta Hospitals
Edmonton, Alberta;
McMaster University
Department of Medicine
Hamilton, Ontario

Effect of Ramipril and Vitamin E on Atherosclerosis
L. Iuliano, F. Micheletta, F. Violi and L.G. Spagnoli

Circulation. 2002;105:e5-e6
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/105/2/e5

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation 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 Circulation is online at:
http://circ.ahajournals.org//subscriptions/