References


To the Editor:
The process by various pathogenetic mechanisms leading to structural or functional changes of the cardiovascular system is currently at the center of interest among investigators. Also the subsequent step, that of evolution from the stage of risk factors to morbid events, is gaining momentum as a research area.\(^1\) The former paradigm is exemplified by the article of Bonithon-Kopp et al.,\(^2\) who examined the association of increased plasma angiotensin-converting enzyme (ACE) activity with thickening of the common carotid wall, expressed as intimal-medial thickness.

I have some questions as to the way the data analysis was carried out: (1) The authors found that ACE activity was not different in their two research cohorts (cases versus control subjects). They then turned to an analysis that excluded patients who were receiving lipid-lowering drugs; this time results pertaining to the ACE were statistically significant. There is a problem conceptually in their analysis. It would have been appropriate to exclude the hyperlipidemic patients to start with, as they did with other traditional risk factors (in "Methods"), since their objective was to focus on the independent effect of ACE activity on carotid wall thickness. The inclusion, therefore, of patients with lipid disorders, while patients with hypertension, diabetes, angina, previous myocardial infarction, and cigarette smoking were excluded, is puzzling.

(2) One may question the validity of using the treatment with antilipidemic drugs as a reason for exclusion of patients from the second analysis. It would have been more appropriate to use the lipid profiles of the patients (total cholesterol, high-density and low-density lipoprotein cholesterol, and triglycerides) for exclusion. The lipid disorder is the risk factor, not the therapy administered to correct it.

(3) In Tables 1 and 2, "ever-smokers" is used in the analysis, while this variable is not previously mentioned; also, systolic and diastolic blood pressures are shown to be statistically significant. In the multivariate analysis, smoking, along with body mass, systolic and diastolic blood pressure, and log ACE appears to be significantly associated with carotid wall thickening. One wonders what would have happened if lipid status in any form was included in the analysis. Is it probable that inclusion of lipids in the multivariate model would render the contribution of the ACE activity to the carotid wall thickening insignificant? Is it probable that lipid status and smoking (either current or in the past) adequately account for changes in the carotid wall dimensions?

John E. Madias, MD
Professor of Medicine
Mt Sinai School of Medicine
Chief Division of Cardiology
Elmhurst Hospital Center
Elmhurst, NY

References


Reply to Dr Madias
The EVA study gave the opportunity to test the hypothesis of a relation between plasma angiotensin-converting enzyme (ACE) activity and carotid wall thickening in an asymptomatic population without any treatment likely to interfere with plasma ACE measurements. Because of the known implication of the renin-angiotensin system in the regulation of blood pressure and the increasing use of ACE inhibitors, it seemed reasonable to exclude subjects who were receiving antihypertensive drugs together with the few others with coronary heart disease and diabetes history. There was no more reason to exclude hyperlipidemic subjects with or without treatment than smokers or obese subjects.

We agree with Dr Madias that statistical analysis by subgroups is questionable if it has not been designed a priori. In fact, our analysis strategy was governed by that of Cambien et al in the ECTIM study. He found that the association between the ACE/I/D polymorphism and myocardial infarction was considerably increased in a low-risk group (including subjects not receiving lipid-lowering drugs and those with low levels of apolipoprotein B and body mass index [BMI]) as compared with the high-risk group. Because of some missing biological data and our small sample size, which would preclude keeping the matched structure for cases and control subjects, we chose to use the consumption of hypolipidemic drugs as the only criterion of exclusion. In parallelism with the observation of Cambien et al, our results suggest that the association between plasma ACE activity and carotid wall thickening might be confined to low-risk subjects. Interestingly, this association was only seen among pairs of subjects without carotid plaques, and this analysis was decided a priori because the number of plaques was a matching criterion for the study.

In the present study, systolic blood pressure, BMI, and smoking (past and current smoking combined) were significantly associated with intimal-medial thickening, whereas no significant association was observed with current smoking, and, for pairs with available data, with total cholesterol and triglycerides. Thus, a further inclusion of total cholesterol and triglycerides in the regression model did not affect the independent association between plasma ACE activity and carotid wall thickening (log ACE regression coefficient ±SE, 2.767 ± 1.261; P < .03; n = 46 pairs). This last result was in fact anticipated, as no correlation has ever been found between plasma ACE activity and lipid levels in cross-sectional epidemiological studies.\(^2\)

References


Reply to Payne et al
The letter of Payne et al gives some results on plasma ACE activity and I/D genotype frequency according to the presence or absence of angiographically proven coronary heart disease. These results are, as far as we are aware, the first ones published in the literature, and some degree of parallelism with ours is striking. However, because of the large clinical heterogeneity of people...
Plasma angiotension-converting enzyme activity and carotid wall thickening.

J E Madias

Circulation. 1994;90:2567
doi: 10.1161/01.CIR.90.5.2567

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/90/5/2567.citation

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