However, the fact that in another study we showed the functional relevance of the same -786C allele in non-Japanese hypertensive patients lends further support to the relevance of this polymorphism for cardiovascular disease in Caucasians (5).

**Gian Paolo Rossi, MD, FACC, FAHA**

**Maurizio Cesari, MD**

**Achille C. Pessina, MD, PhD**

Department of Clinical and Experimental Medicine
Clinica Medica 4 University Hospital
via Giustiniani, 2
35126 Padova
Italy
E-mail: gianpaolo.rossi@unipd.it

doi:10.1016/S0735-1097(03)00890-8

**REFERENCES**


**Response to Renin-Angiotensin System Antagonists in Hypertensive Black Subjects**

We read with interest the study by Flack et al. (1) which appeared in the April 2, 2003, issue of the Journal. We commend the researchers on investigating the effects of aldosterone antagonism in the black population, who are traditionally underrepresented in clinical trials. However, we have some concerns regarding the characteristics of the study subjects.

First of all, we question the investigators’ use of weight, rather than body mass index (BMI), as an anthropometric measurement. Data from the Framingham Heart Study indicate that higher BMI is a major determinant of inadequate blood pressure control with antihypertensive medications (2). Though not statistically different, both male and female subjects in the eplerenone group had greater body weight than did those in the losartan group. Thus, we are curious as to whether BMI differed between treatment groups and, if so, whether these differences may have contributed to the disparity in results between groups.

Second, the study included participants from both the U.S. and Africa. The investigators do not report the percentage of black participants who were from Africa versus those from the U.S. This information is important in conferring the applicability of the study findings to blacks in the U.S. Differences in environmental factors have been reported among populations of African origin, with higher BMI and greater sodium intake reported among American blacks compared to African blacks (3). Similar to BMI, sodium intake is a well-known factor influencing antihypertensive response to renin-angiotensin system antagonists (4–6). Thus, whether aldosterone antagonism would produce similar antihypertensive effects in black Americans compared to black Africans is uncertain.

**Larisa M. Humma, PharmD**

**Patricia L. Adenekan, PharmD**

University of Illinois at Chicago
College of Pharmacy
Department of Pharmacy Practice
833 S. Wood
Room 164
Chicago, IL 60612
E-mail: humma@uic.edu

doi:10.1016/S0735-1097(03)00895-7

**REFERENCES**


**REPLY**

We appreciate the questions raised by Humma and Adenekan regarding the potential impact of body mass index (BMI) on the blood pressure (BP)-lowering differences between eplerenone and losartan in our recently published study. Also, the relevance of the BP-lowering obtained in South African blacks to U.S. blacks was raised.

There were 335 black participants in our trial; 260 (77.6%) resided in the U.S. and 75 (22.4%) in South Africa. Black participants were approximately evenly dispersed across treatment groups with randomization to placebo, eplerenone, and losartan in the following numbers (U.S. blacks/South African blacks): 1) placebo (86/24); 2) eplerenone (83/25); and 3) losartan (91/26). Blood pressure responses (SBP/DBP mm Hg) at 16 weeks (end of trial) for blacks were: 1) placebo (−3.7/−4.8); 2) eplerenone (−13.5/−10.2); and 3) losartan (−5.3/−6.0). Among South African blacks, BP changes were: 1) placebo (−1.1/−1.3); 2) eplerenone (−11.6/−10.1); and 3) losartan (−0.8/−3.6). The overall rank-order of BP response was the same among U.S. and South African blacks, although the absolute magnitude of change...
did appear to differ. Nevertheless, we believe that our reported findings are relevant to U.S. blacks given the same rank-order of BP responses within each group as well as the fact that the majority of black participants were from the U.S.

We agree with Drs. Humma and Adenekan that dietary sodium intake and body size may potentially confound BP changes to pharmacological agents. We (1) and others (2,3) have shown that higher levels of dietary sodium intake attenuates the BP lowering effect of antihypertensive agents, especially drugs working primarily on the renin-angiotensin-aldosterone-kinin system. The study participants in our trial were not counseled to restrict dietary sodium intake nor was urinary sodium excretion measured. Thus, the effect of dietary sodium by region, ethnic group, or drug treatment cannot be determined. Conversely, it is plausible that high levels of dietary sodium may have attenuated the BP lowering effect of losartan moreso than eplerenone.

We also agree that body size can influence BP change to pharmacological interventions. In fact, this is an underrecognized factor influencing treatment responses (4,5). The body weights (weighted for the proportions of men and women) in the losartan and eplerenone groups, respectively, were 91.9 kg and 88.7 kg, which corresponds to a difference of 3.2 kg. When BMI levels are compared, no difference existed between the eplerenone and losartan groups in men and only a very small difference in women. Median BMI levels in women randomized to eplerenone and losartan, respectively, were 32.1 and 33.8 kg/m²; in men, median BMI rates for the same two groups were 29.7 and 29.6 kg/m², respectively. We do not believe that these very slight differences in body size account for the BP response differences between eplerenone and losartan that we reported.

In conclusion, the questions raised are certainly important. However, we do not believe the relatively modest body size differences, as determined by any metric, explains our results to any significant degree. Finally, assuming that high levels of dietary sodium intake importantly influenced BP responses, our data suggest that eplerenone lowers BP more robustly in American and South African blacks than does losartan in high-sodium-consuming hypertensives.

John M. Flack, MD, MPH
Department of Internal Medicine
Wayne State University
4201 St. Antoine
2E UHC
Detroit, MI 48201
E-mail: JFlack@intmed.wayne.edu

Scott L. Krause, BSN
Suzanne Oparil, MD
J. Howard Pratt, MD
Elijah Saunders, MD

Neopterin—A Forgotten Biomarker

In a recent issue of the Journal, Blake and Ridker (1) summarized findings regarding the prognostic role of C-reactive protein (CRP) and other inflammatory markers in patients with acute coronary syndromes (ACS). We would like to point out that the investigators did not include the role of neopterin in this context. Neopterin (2), a pteridine derivative and a by-product of the guanosine triphosphate–bipterin pathway (3), is produced by activated macrophages and represents a marker of immune activation. Studies from our group (4) and others (5,6) have shown that circulating neopterin levels are higher in patients with ACS compared to patients with a history of myocardial infarction, patients with stable angina pectoris, or control subjects. High neopterin levels may be a marker of coronary disease activity, as suggested by its association with angiographically complex lesions in patients with unstable angina (7) and its role as a marker of future cardiovascular events in women with coronary artery disease (CAD) (8). The prognostic significance of neopterin in ACS patients has been reported by Auer et al. (9), albeit in a small group of patients. Preliminary prospective work from our unit has recently shown that, in patients with CAD, serum neopterin is an independent predictor of major adverse coronary events at one-year follow-up (data not published).

Finally, although convincing evidence exists regarding the prognostic value of inflammatory markers in patients with ACS, the independent and/or complementary role of different biomarkers has not been systematically investigated in large prospective studies. The ongoing SIESTA (Systemic Inflammation Evaluation in patients with non-ST-segment elevation Acute coronary syndromes) study (10)—a prospective multicenter trial designed to assess the relative prognostic role of diverse markers of inflammation, including, among many others, CRP, neopterin, cell adhesion molecules, and pregnancy-associated plasma protein A—will help to elucidate the issue.

Juan Carlos Kaski, MD, DSc, FRCP, FESC, FACC
Department of Cardiological Sciences
Director of Coronary Artery Disease Research Unit
St. George’s Hospital Medical School
London SW17 0RE
United Kingdom
E-mail: jkaski@sghms.ac.uk

Pablo Avanzas, MD
Ramón Arroyo-Espliguero, MD