EDITORIAL COMMENT
Hypertension, Angiotensin II, Aldosterone, and Race*

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One in four Americans has hypertension. Improvements in hypertension awareness and treatment in the 1970s and 1980s have contributed to a nearly 60% decline in the age-adjusted death rates from stroke. Still, since 1993, stroke rates have risen, along with the prevalence of heart failure and end-stage renal disease (1). Moreover, in approximately two-thirds of hypertensive patients, blood pressure (BP) is not fully controlled. The challenge of hypertension is particularly severe in the African American community, which is disproportionately affected. Not only is the prevalence higher (32% of African Americans vs. 23% for non-African Americans), but also the complications of uncontrolled high BP are up to four times more frequent in African Americans (2-4). Treatment gaps are also greater in the African American population.

The availability of a novel aldosterone inhibitor comes at a time of renewed attention to the role of aldosterone in cardiovascular disease (6). Aldosterone receptors have been linked in animal models with both vascular and myocardial fibrosis (7). In both patients with hypertension and patients with heart failure, aldosterone levels are elevated despite complete long-term inhibition of vascular angiotensin-converting enzyme (ACE), pointing to a phenomenon of aldosterone escape (8). Whether aldosterone escape occurs in the setting of ARB use is unclear, particularly in humans, with one animal study suggesting that it does not (9).

News of more efficacious treatments of hypertension, in general, and in African Americans in particular, is, of course, to be welcomed, and the results of monotherapy with eplerenone in this study confirm its efficacy. The relative lack of efficacy of losartan as monotherapy in black patients documented in the study by Flack et al. (5) is not surprising, as black hypertensive patients, who are more likely to have low renin levels, are known to be less responsive to monotherapy with ARBs as well as ACE inhibitors (10). Indeed, in a previously published study of 440 hypertensive African Americans, Flack et al. (11) demonstrated that losartan monotherapy (titrated up to 150 mg/day) reduced sitting diastolic blood pressure (DBP) by only 6.6 mm Hg and systolic blood pressure (SBP) by 6.4 mm Hg (11). Moreover, losartan monotherapy had a flat dose-response curve in this population. When low-dose hydrochlorothiazide (12.5 to 25 mg) was added to 50 to 100 mg of losartan, however, BP reductions of 10.8 mm Hg in DBP and 16.8 mm Hg in SBP were achieved. Therefore, although monotherapy with losartan (and presumably other ARBs as well) is unlikely to achieve adequate BP reductions in the low-renin African American hypertensive patient, the addition of a low-dose diuretic can robustly lower BP. The use of a diuretic is particularly important in the salt-sensitive low-renin patient who continues to consume a high-sodium diet.

In this issue of the Journal, Flack et al. (5) report on the efficacy and tolerability of a novel antihypertensive agent, the selective aldosterone antagonist eplerenone, which was recently approved by the Food and Drug Administration for the treatment of hypertension. In the study by Flack et al. (5), eplerenone was tested (at 50 to 200 mg/day) versus placebo, as well as versus the angiotensin receptor blocker (ARB) losartan (at 50 to 100 mg/day), in hypertensive black patients (because the trial included patients in South Africa as well as the U.S., the term black rather than African American was used to describe the study population). The effects of the two agents as monotherapy on black patients were also compared with the effects on white patients. Although the two agents had similar efficacy in white patients, eplerenone was significantly more efficacious than losartan in black patients.

The availability of a novel aldosterone inhibitor comes at a time of renewed attention to the role of aldosterone in cardiovascular disease (6). Aldosterone receptors have been found in the brain, myocardium, and vasculature, and aldosterone has been linked in animal models with both vascular and myocardial fibrosis (7). In both patients with hypertension and heart failure, aldosterone escape occurs in the setting of ARB use is unclear, particularly in humans, with one animal study suggesting that it does not (9).

Reduction in BP can be viewed as a surrogate end point. Ultimately, the results of therapy on morbidity and mortality are of much greater importance. In this regard, the recently published Losartan Interventions For Endpoints reductions (LIFE) study (12) sheds important light on the importance of angiotensin II and its blockade and points to potentially important differences among BP medications beyond reductions per se in BP. In the LIFE study, the efficacy of a losartan-based regimen was compared with an atenolol-based regimen in 9,193 patients with hypertension.

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and left ventricular hypertrophy (LVH). Although BP reductions were identical in the two active treatment arms, losartan was superior to atenolol with greater regression in LVH and a 25% reduction in stroke.

The results of the LIFE study, conducted against an active beta-blocker comparator, point to the importance of angiotensin II and its blockade in cardiovascular disease. Angiotensin II has been implicated in endothelial dysfunction, oxidative stress, medial arterial hypertrophy, LVH, and atherosclerosis among others (13). Blockade of angiotensin II at its type 1 (AT-1) receptor has been shown to improve endothelial function, reduce arterial medial hypertrophy (14), and in a primate model, markedly reduce atherosclerosis (15). Thus, theoretical, experimental, and outcome data exist to support inhibiting the renin-angiotensin system.

However, the situation in African Americans is more complicated. As a group, African American hypertensive patients have lower plasma renin activity and are more salt-sensitive, with diminished pressure natriuresis response. Intrarenal levels of angiotensin II are, however, actually increased. Though the reason for this is unclear, it is consistent with the finding in the LIFE study, wherein losartan was superior in black patients who comprised 6% of the study population, atenolol was superior (17). Given the relatively small sample size, larger studies need to be done to address this issue.

Treatment with aldosterone antagonists results in an increase in renin levels and, conceivably, in angiotensin II. While animal data suggest that some of the effects of angiotensin II outside the kidney are mediated by aldosterone, whether outcomes with a drug such as eplerenone would be comparable to those seen with ACE inhibitors and ARBs remains to be established. Moreover, the concomitant use of aldosterone blockade with ARB or ACE blockade has yet to be fully addressed. Conceivably, combination therapy with both eplerenone and an ARB or ACE inhibitor would provide for more complete neurohormonal blockade. Hyperkalemia, however, a well-recognized side effect of both eplerenone and ACE/ARBs, was increased in combination studies. Particularly in diabetics with albuminuria there was an unacceptably high incidence of hyperkalemia with eplerenone therapy alone or in combination with ACE inhibition (18). Although aldosterone blockade with spironolactone has gained acceptance in combination with ACE inhibition in the treatment of heart failure, the less frequent monitoring given to patients with hypertension compared with patients with heart failure mandates caution in using ACE/ARBs in combination with aldosterone blocking agents such as eplerenone in the treatment of hypertension even in the non-diabetic. Given the disparities in health care access, this issue is particularly relevant in the African American population.

The advantage of eplerenone over the aldosterone antagonist spironolactone, which is also indicated for the treatment of hypertension, is in its greater selectivity. In vitro, eplerenone was shown to be highly selective for the aldosterone receptor, with low binding to progesterone (<1%) and androgen (0.1%) receptor (19). Thus, whereas spironolactone is associated with a gynecostasia of 6.9% in hypertensive males, the incidence of gynecostasia or mastodynia was 1.6% in eplerenone studies (18) lasting longer than six months. In females, abnormal vaginal bleeding was reported in 0.8% on eplerenone in controlled studies lasting >6 months, and in 2.1% in open-label, long-term studies. Thus, while the side effect profile of eplerenone is decidedly more favorable than spironolactone, the potential for hormonal side effects is not entirely eliminated.

Finally, important but thorny issues regarding the use of race in clinical studies are raised by the study by Flack et al. (5). Some have criticized studies that use skin color and self-designation of racial affiliation as being instances of "racial profiling" (20). Still, it is undeniable that disease prevalence and responses to therapy often differ in different ethnic and racial populations, with hypertension and its effects in African Americans being a prime example. Recently, the increased incidence of two synergistic polymorphisms of the beta1- and alpha2c-adrenergic receptors in black patients allowed researchers to link the presence of these polymorphisms to a markedly increased risk of the development of heart failure (21). Indeed, the increased frequency in blacks of polymorphisms affecting the adrenergic system may explain their overall better response to therapy with beta-blockade versus ARBs as seen in the LIFE study. Similarly, whereas carvedilol was equally efficacious in white and black patients with heart failure (22), enalapril was less effective in black patients compared with white patients (23). Indeed, it is precisely because of these differences that researchers are mandated to enroll a racially diverse population in clinical studies.

Whether a study is primarily aimed at studying a specific racial group versus another or subgroup analysis is used to assess the response in different racial populations, important and potentially useful clinical information is generated. That there are differences between racial groups in prevalence of disease or in response to therapy is ultimately, however, due to the different frequency of genetic and environmental factors among different groups. The use of racial designations in clinical studies is only an imprecise and problematic surrogate for genetic polymorphisms as well as the social, economic, and other factors that may influence biology. Therefore, there is a risk, particularly in the genetically very heterogeneous population of the U.S., of assuming a certain biologic effect simply on the basis of race.

The genetic revolution may ultimately provide us with the tools to determine the best therapy for a given patient in a racially blind manner. We could then tailor therapy based
on individual determinants rather than racial and social ones. In the meantime, we should be cautious in our application of results based on race-based studies in clinical practice.

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