From Black and White to Shades of Gray
Race and Renin-Angiotensin System Blockade*

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In this issue of the Journal, Prisant et al. (1) present a retrospective subgroup analysis of data from the VALIANT (Valsartan in Acute Myocardial Infarction Trial) study in which they show comparable outcomes for African-American and white patients with left ventricular dysfunction after a myocardial infarction regardless of the treatment assigned. The results of this analysis have important implications for the treatment of patients after a myocardial infarction, for the use of renin–angiotensin system (RAS)–blocking agents for African Americans with hypertension and heart failure, and for race-based treatment in general.

The parent study enrolled 14,703 patients in 24 countries; participants had had a myocardial infarction and had either clinically apparent heart failure or a reduced ejection fraction. Subjects were randomized to receive valsartan, captopril, or a combination of these. Overall, the 3 treatments had statistically indistinguishable effects on cardiovascular events and on all-cause mortality.

The current study is of the U.S. subset of 3,390 white and 340 African-American patients. In agreement with previous comparisons by race of patients with heart failure, African-American patients were younger, more likely female, and more likely to have hypertension and diabetes. The investigators compared African-American and white patients by treatment group with regard to subsequent all-cause and cardiovascular mortality, heart failure hospitalizations, myocardial infarction, and stroke. Multivariable regression was used to adjust the outcomes for the racial differences in baseline characteristics. For all end points studied, there were no interactions between race and treatment assignment.

Some may find these results surprising. There is a widely held view that African Americans with hypertension and heart failure do not have a response to angiotensin-converting enzyme (ACE) inhibitors, which has some basis in evidence from randomized trials. Exner et al. (2) analyzed outcome data from the treatment and prevention arms of the SOLVD (Studies on Left Ventricular Dysfunction) by race. Black subjects had slightly higher blood pressure at baseline. Despite uniform treatment across race with approximately 15 mg/day enalapril, blood pressure decreased significantly in the white subjects but did not change in the black subjects. In white subjects, enalapril treatment reduced the rate of heart failure hospitalizations, whereas in black subjects there was no effect. Similar results were reported in an analysis of data from the ALLHAT (Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) study by race (3). The relative risk for incident coronary heart disease, stroke, and heart failure was significantly greater for black subjects treated with lisinopril compared with those treated with chlorthalidone; for nonblack subjects the differences were not significant. As in the SOLVD study, blood pressure response to the ACE inhibitor was significantly less in black compared with nonblack patients.

On closer examination, however, the racial differences in outcomes in these studies are not quite as stark. In the SOLVD study, the effect of enalapril treatment on all-cause mortality was the same in black and white subjects; treatment was not associated with a reduction in mortality in either group. There are probably 2 reasons for the discordance between the heart failure result and the mortality result. First, the rate of hospitalization for heart failure end point is much more likely to be affected by unmeasured confounding. Need for hospitalization is affected by factors such as insurance status and access to care, where African Americans are at a disadvantage. Second, the sample size seems to be too small to support the desired analyses. The finding that enalapril did not reduce mortality in either racial group contradicts clear and consistent findings that ACE inhibitors improve outcomes in patients with left ventricular dysfunction, and is almost certainly caused by the numbers of observations being too small to detect small differences in outcome.

In the ALLHAT study, a formal test of interaction between race and treatment for predicting heart failure was not significant. A negative finding on this more stringent test suggests that racial differences in response to ACE inhibition in heart failure prevention are quite small if present at all.

The best way to understand these findings is to view both African-American and white patients as having wide intra-group variation in response to ACE inhibition. Although the mean response between the groups might be slightly...

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different, the individual responses overlap substantially. This view is illustrated by the results of a study of perindopril monotherapy for hypertension (4) in which blood pressure control was achieved in approximately 40% of African-American and 50% of white patients at 12 weeks. The notion of substantial overlap in individual response is consistent with findings that show that African Americans and white Americans are not as different genetically as we might be conditioned to believe. In one recent study using 2,154 single-nucleotide polymorphisms (5), the median percentage of European ancestry in a group of African Americans was estimated to be approximately 25%, and was even >50% in a small subgroup. As our knowledge of the human genome expands, race is being seen increasingly as a mutable characteristic of human populations. A recent analysis of the HapMap database (6) suggests that the wide variability in human characteristics we use the term race to describe is a relatively recent development, occurring over the past 40,000 years, with the rapid acceleration in human evolution resulting from explosive growth and spread of the population.

In the case of RAS blockade, wide variation in individual response likely results in a situation in which a majority of white and African-American individuals has a vigorous response to RAS-blocking agents and a larger minority of African-American patients has a muted response. It seems to be possible to circumvent this muted response easily. When upward titration of dose or addition of diuretics is allowed in clinical trials, differences in response to RAS blockade by race diminish. For example, in a study of telmisartan in patients with hypertension in which concomitant use of diuretics was allowed (7), rates of hypertension control were similar for black and white patients despite similar telmisartan doses; black patients were more likely to receive concomitant diuretics.

The results of the current study should be interpreted and applied to the care of patients with left ventricular dysfunction after myocardial infarction with this background in mind. The results do not suggest that angiotensin receptor blockers offer advantages over ACE inhibitors for African Americans; both drug classes should be viewed as effective regardless of race. Therapy should be modified for individual response regardless of race. Although African-American patients in the VALIANT study were more likely at follow-up to be on diuretics. Adding a diuretic when blood pressure remains unchanged might improve effectiveness, but more data are needed before this approach can be recommended. Finally, it should be recognized that the number of African-American patients studied was relatively small and that race—treatment interaction may have been significant if the sample size had been larger.

There are disparities by race in the U.S. in the incidence of potentially preventable cardiovascular disease, in the evaluation and treatment of cardiovascular disease, and in the outcomes of cardiovascular disease. Possible sources for these disparities include the health consequences of inequality in education and employment, the effects of prejudice, and the inability to measure and act on differences in genetic determinants of disease and response to treatment. Seen in this light, there are 2 problems with race-based therapy as a strategy for addressing racial disparities. First, this strategy ignores and diverts attention from social determinants of disparities. Second, this strategy is an overly crude substitute for measuring individual variability in genetic predisposition to disease and response to therapy. The current study illustrates this point well; known differences in response to RAS blockade by race were simply not great enough to result in a detectable difference in outcomes.

Differences in response to drug treatments by race are not stark but subtle—not black and white but shades of gray. Until these subtle shadings can be measured more precisely through individual genotyping, race-based therapy should be approached with caution, if at all.

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