

VIEWPOINT

Prescribing BiDil

Is It Black and White?

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The approval of BiDil as an adjunct treatment in self-identified blacks with heart failure raises questions regarding the underlying etiology of drug response in this target population and the ability to accurately identify patients who are most likely to benefit. Preliminary data have indicated that differences in nitric oxide synthesis between groups may account for differences in response to BiDil and genetic studies have begun to elucidate the mechanism of these differences. Until more accurate selection criteria are developed to identify patients who are most likely to benefit, both clinicians and the general public will need to consider the unique issues raised by BiDil. (J Am Coll Cardiol 2006;48:12-4) © 2006 by the American College of Cardiology Foundation

With the push toward personalized medicine, the approval of a drug that uses race as an identifier to enrich a target population seems counter to the vision for the future of medicine. In contrast to targeted therapies such as herceptin or gleevec that use protein or genetic biomarkers to identify individuals likely to benefit from treatment, the approval of BiDil as an adjunct treatment in “self-identified blacks” with heart failure (HF) continues to rely on the practice of population-based medicine. Although the field of cardiology has proved more challenging in identifying genomic markers predictive of disease, outcome, or drug response, the use of race may be a step backwards in the area of targeted therapies. The approval by the U.S. Food and Drug Administration (FDA) of BiDil occurs at a time when scientists and the medical community continue to debate the biological significance of race (1-4) and its use in medical practice (5,6). The fallout or consequences of these developments are unclear from a scientific, clinical, and social perspective.

Among the questions raised by this approval are whether race is a surrogate for underlying biology that explains the benefit in some blacks, and secondly whether physicians can truly identify patients who are most likely to benefit from the drug using race as the selection criterion. BiDil is a fixed-dose combination of isosorbide dinitrate and hydralazine hydrochloride (20 mg/37.5 mg). Initial studies showed the efficacy of the combination treatment when compared with placebo and another vasodilator (prazosin) (7) and with enalapril (8) in men (both black and white) receiving digoxin and diuretic therapy for HF. Application for FDA approval based on these data for the combination treatment for the general population was rejected.

Subsequent retrospective data analysis, however, suggested an improvement in mortality in black patients on combination treatment, whereas white patients showed no benefit over placebo or showed greater benefit from enalapril compared to the combination treatment (9). After consideration of these data, the FDA indicated that a persuasive clinical study limited to black HF patients could serve as the basis for approval of BiDil. This third study, the A-HeFT (African-American Heart Failure Trial), was designed to confirm the response of combination treatment added to standard therapy in black HF patients (10). The trial was terminated early owing to the statistically lower mortality rate in patients receiving the isosorbide dinitrate/hydralazine combination compared with placebo (11).

Race is presumed to be a *surrogate* for the true basis of these observations. Disparate observations in drug response between black and white populations with HF may be due in part to biological, environmental, and/or sociocultural factors subsumed under the variable of race. In order to identify the variables responsible for efficacy of BiDil in blacks, factors from each of these categories will need to be characterized in patients who do and do not respond to BiDil in different populations.

Differences in gene allele frequency among ethnic groups have been known for decades. In genes implicated in heart disease, for example, frequencies of gene variants in paraoxonase 1 (12), angiotensin-converting enzyme (13), and the adenosine triphosphate-binding cassette reporter 1 (14) have been found to differ significantly between blacks and whites. Given that BiDil works by enhancing production and stability of nitric oxide, it has been hypothesized that reduced nitric oxide bioactivity seen in blacks may account for the improved response to BiDil (15,16). The frequency of several genetic variants in the endothelial nitric oxide synthase gene have been shown to vary between black and white populations, however, the clinical significance of this finding is unclear (17). For example, the G894T variant has

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
FDA = Food and Drug Administration
HF = heart failure

been found to be significantly associated with measures of lower arterial wall stiffness in blacks (18). However, the intronic 4a variant was found to be highest in both black and white patients with multivessel disease evaluated from a group of 194 patients undergoing coronary angiography although no correlation was detected between the variant and endothelial function (19). A recent presentation at the American Heart Association's annual meeting showed data demonstrating an association between the G894T variant and BiDil response (20). Validation of this data may provide additional criterion for predicting drug efficacy.

Although the consideration of race in the decision to prescribe certain medications is not new, BiDil is the first drug specifically targeted to a single population based on a clinical trial composed solely of members of that population. Given that BiDil is indicated as an adjunct treatment in "self-identified blacks" with HF, *how should clinicians decide who is to be prescribed BiDil?* In the U.S., "black" is often used synonymously with African American. In contrast, in the United Kingdom, black may indicate Black Caribbean, Black African, or individuals from the Indian subcontinent. In addition, previous work has demonstrated a range of mixed ancestry in African Americans, Hispanics, and Mexicans (21). In the 2000 U.S. census, more than six million Americans reported two or more races. The use of self-identification is problematic, because it has not always been shown to be a consistent and reliable measure (22). In the 1970s, the U.S. Bureau of the Census examined the reliability of self-reporting by interviewing a sample of household members twice over two years (23). Between the two interviews, the ethnic identities changed in more than 34% of the household members. In addition, the context in which the self-identification is made may influence an individual's decision, resulting in variable responses depending on who is asking the question and how the information might be used (24). Although self-identified race has been shown to correspond highly with genetic clustering (25), the percent of genetic ancestry varies widely (26). These ambiguities highlight the need for more precise measurements to identify those who will benefit from BiDil.

The social implications of targeting BiDil to a single racial group may validate and/or increase race-based medical practices and create divisions of "white" and "black" drugs in the public's mind-set. Since the limitations of the dataset from the BiDil studies may not be obvious to the general public or health professionals, enhanced communication is needed about the safety and efficacy of the drug in black and other populations. By far, the case of BiDil does not resolve the debate about the biologic significance of race, but in fact

provides an opportunity to further clarify the association of race with drug response. As the biologic underpinnings of disease, drug response, and interaction with environmental variables continue to be studied, clinicians will need to consider the unique challenges raised by BiDil and recognize the limitations of current knowledge. We look forward to the day when the data are available to support the use of a particular molecular genotype to identify individuals who are likely to benefit from BiDil.

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