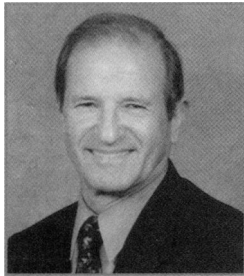


# What's Right (and Wrong) with Racially Stratified Research and Therapies

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**Key words:** ACE inhibitors ■ race/ethnicity

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## BACKGROUND

In June 2005, BiDil®, a fixed-dose combination of isosorbide dinitrate and hydralazine hydrochloride (i-h), became the first drug approved by the Food and Drug Administration (FDA) for use only in a specific population of individuals who self-identify as black (defined as of African descent).<sup>1</sup> This announcement was greeted by rounds of applause and approval from medical professional groups and the lay public—and negative reactions from others, ranging from cautionary statements to outright condemnation. Over the past year, the question of whether drug research that focuses on a specific self-identified race should be done at all has been a subject of spirited debate in the medical literature and lay media. The randomized clinical trial (RCT) that

convinced the FDA to approve BiDil arose from several earlier studies, especially the Vasodilator Heart Failure Trials (V-HeFT).

The first V-HeFT (V-HeFT I) demonstrated the effectiveness of i-h in treating heart failure.<sup>2</sup> A second study, V-HeFT II, compared the effectiveness of this combination with the angiotensin-converting-enzyme (ACE) inhibitor, enalapril.<sup>3</sup> It showed that enalapril was associated with a greater overall reduction in mortality than i-h. A subgroup of patients, however, did not do as well on enalapril as they did on i-h. A biotechnology company, NitroMed Inc., obtained intellectual property rights to a fixed-dose combination of i-h (BiDil), but in 1996, the FDA did not approve marketing this combination as a new drug because of lack of proof of its effectiveness.<sup>4</sup>

Reanalysis of the data from the earlier V-HeFT I & II, this time stratifying by race, as the subjects identified themselves, found that the combination treatment was just as effective in prolonging the lives of black patients with heart failure as ACE inhibitors were in whites.<sup>5</sup> The FDA indicated that if a clinical trial confirmed the effectiveness of BiDil in blacks, approval of the drug specifically for black patients with severe heart failure would probably follow.<sup>4</sup>

A new RCT was designed and carried out in 2001–2004, the African-American Heart Failure Trial (A-HeFT).<sup>6</sup> This trial studied BiDil combined with conventional therapy for heart failure (which by that time included an ACE inhibitor) compared with conventional therapy alone.<sup>4</sup> The Association of Black Cardiologists and NitroMed cosponsored the study, which was limited to self-identified blacks who suffered from NYHA class-3 or -4 heart failure. In 2002, NitroMed was granted a new patent, based on the use of BiDil specifically in black patients. This was the first patent ever granted for a new drug limited to use only in one race. The original patent was to expire in 2007, but the new patent pushed back the expiration date to 2020, preventing generic drug companies from manufacturing and selling i-h for an additional 13 years.

A-HeFT studied 1,050 patients and showed that BiDil, when combined with standard therapy, increased survival in

the study group by 43% compared with standard treatment alone. The study group also had a 33% greater reduction in the rate of hospitalization for heart failure and significantly greater improvement in quality-of-life measures.<sup>6</sup>

The FDA announcement of BiDil approval cited the facts that 750,000 black patients suffer from severe heart failure, and those in the age range of 45–64 years carry a 2.5 times' greater risk of death than similarly situated white patients. There is no cure for severe advanced heart failure; 50% of the patients who have the disease die within five years.<sup>1</sup> The National Medical Association commended the FDA for approving the use of BiDil in blacks.

The FDA approval of BiDil for use in blacks elicited a range of approving statements.<sup>7</sup> "I take anything that shows a benefit for heart failure as an advance" (Keith Ferdinand, a member of the Association of Black Cardiologists); "Today's approval of a drug to treat severe heart failure in self-identified black population is a striking example of how treatment can benefit some patients even if it does not help all patients" (Robert Temple of the FDA); "In BiDil, we now have a treatment that has been shown to save the lives of black heart failure patients, helping a population that is disproportionately burdened by cardiovascular disease" (Anne Taylor, lead A-HeFT investigator).<sup>8</sup>

At first blush, it seems odd to find fault with research that can lead to such positive results. But critics of the study and of the FDA approval of the drug for use only in blacks found plenty to criticize. The criticisms are, to some extent, valid, but some are aimed at the wrong target, and some are true but not relevant to this issue. Considering all of the criticisms together, they are not, in my opinion, sufficient to condemn the BiDil study nor to inhibit similar race-based research in the future.

The objections can be roughly divided into three general categories, with much overlap between them: biological-scientific, marketing-financial and social, as discussed below.

## Biological and Scientific Issues

*A fundamental scientific problem with the idea of doing research stratified by race is the claim that the very concept of race is biologically meaningless: "Race is a social construct, not a scientific classification." Therefore, there should be a "requirement to furnish a scientifically valid definition of the population under study."*<sup>9</sup> It is certainly true that race is not a scientific classification, and it may be largely socially constructed. This does not mean, however, that race is biologically meaningless. Biological differences among races and ethnic groups have been well documented. For example, although no polymorphic trait is unique to a particular racial group, certain variants occur at different frequencies in different populations. CYP2D6, the cytochrome P-450 enzyme that is responsible for the metabolism of beta-blockers and tricyclic antidepressants, is functionally absent in 8% of whites but in <1% of Asians, lead-

ing to different drug responses in these populations. CYP2D6 in Africans and African Americans frequently has impaired activity and is encoded by an allele that is virtually absent in white and Asian populations.<sup>10</sup> This particular genetic difference may have contributed to some of the differences in outcomes of the studies that lead to the approval of BiDil. Thus, there are at least some biological differences between races and ethnic groups that may justify stratification of clinical trial groups by self-identified race, even if a "scientifically valid definition" of the study groups is not available.

*Race is a very crude marker, and using self-identification as a member of a particular race is particularly problematic, leading to a highly heterogeneous group for study. More specific markers, based on genes associated with diseases should be used in such studies.*<sup>4</sup> Self-identification as a member of a particular race confounds clinical studies for many reasons. For example, a substantial proportion of the American population is of mixed racial origin, so the same person may self-identify in two, three or more racial groups. This is bound to lead to highly heterogeneous racial groups for study. More specific markers, such as the presence or absence of the specific enzymes or genes associated with diseases, should be used whenever possible in stratifying study groups. Yet, until we know what the specific markers are and can identify them fairly easily, we must use more approximate markers. In the HeFT series of studies, self-identification by race was undoubtedly not the most precise marker to use, but the investigators did not have a better one. Despite the imperfections of racial stratification in the V-HeFT studies, significant and important differences between whites and blacks were found, differences that led to A-HeFT, and, ultimately, to an important new treatment that works well in treating heart failure in self-identified blacks.

*There is no reason to assume that a drug will work for all people in a particular group when it should be perfectly obvious that people in other groups also might benefit.*<sup>4,11,12</sup> That is a true statement; not every black with advanced heart failure will benefit from BiDil, and some whites and Asians will also benefit. The fact that people other than blacks might benefit was clearly recognized by the investigators of A-HeFT: "A future strategy would be to identify genotypic and phenotypic characteristics that would transcend racial or ethnic categories to identify a population with heart failure in which there is an increased likelihood of a favorable response to such therapy."<sup>6</sup> This study clearly is only the first step in a needed series of studies to delineate the biological markers that will identify those most likely to benefit from BiDil. The fact that more work is needed does not suggest either that this study should not have been done or that future studies of specific races or ethnic groups would not be warranted. The path taken by research that produces medical and biological advances is never straight, but neither is it

a random walk. Most research advances our knowledge base in the correct general direction, and an occasional study leads backwards. The BiDil study clearly demonstrated a new way to save lives and to improve quality of life for many blacks; it took us a step forward toward treating heart failure. Future research will give us better and more sharply focused tools to identify patients who are likely to benefit from specific therapies.

## Social Issues

*Differences in pathophysiology and responses to drugs among groups of people may be based on factors other than genetic, such as a mixture of socioeconomic, cultural, psychosocial and environmental factors. Focusing on race may discourage investigation of these nongenetic factors.*<sup>4</sup> It is certainly true that pathophysiology and responses to drugs may be based on many factors other than genetic, including those cited above. Research into disparities in healthcare has investigated the role of just such factors in healthcare outcomes, and we have learned much from those studies, yet a great deal remains unknown. In view of the widespread, active interest in elucidating the causes and prevention of disparities in healthcare outcomes, it seems implausible that investigations that stratify populations by race will discourage investigation of nongenetic factors in healthcare outcomes.

*Official governmental approval of a drug that is specifically designated only for blacks will bolster the repugnant and discredited notion that blacks and whites have fundamental biological differences.*<sup>7</sup> The scars in our social fabric from the wounds inflicted by the Tuskegee experiment persist and still cause considerable concern and discomfort when race is mentioned in the context of healthcare, especially within the black community. Yet, not even the most radical critics of the BiDil drug trials have suggested any similarity to the Tuskegee study; still, discomfort over race-based investigations is understandable. Tuskegee is not the only reason for concern in this regard, as studies of healthcare outcomes have provided a continuing stream of evidence of differential outcomes that disfavor blacks. Much needs to be done to correct these well-documented disparities in healthcare. FDA approval of BiDil suggests biological differences between races, and the existence of such differences is well known. The known variations, however, are confined to a few genes and proteins that do not constitute “fundamental biological differences.” What we must do is to treat genetically determined differences among races, ethnic groups and other demographic subdivisions as socially neutral: the fact that whites respond better to enalapril than do blacks does not make them either inferior or superior, nor does the fact that blacks respond better to BiDil make them superior or inferior. Concerns about misinterpretation and misuse of biological facts are well grounded, but, in view of the powerful benefits of BiDil to blacks, such concerns should be used neither

to condemn research stratified by race nor to denounce the action of the FDA in approving BiDil.

## Financial and Marketing Issues

*No RCT with stratification by race has ever been done that specifically compares i-h with ACE inhibitors, so we do not know if there is truly a difference among races. Rather than a study of blacks only, all patients should have been studied. The black population was specifically studied because the company, NitroMed, knew and cynically used the differences between races found retrospectively in V-HeFT II merely to gain an additional 13 years of patent protection that would otherwise not have been allowed. A-HeFT was motivated not so much by the best science as by regulatory and market incentives.*<sup>4,13</sup> The facts underlying this criticism are true, but the inferences drawn from them miss the mark. While many speak of regulatory and market incentives pejoratively, government has intentionally—for what it has viewed as the public good—made these factors substantial motivators of research and development in the drug industry (as well as most other industries). While some may wish it to be otherwise, the main purpose for the existence for any business is to make money for its owners.<sup>14-16</sup> The purpose of profits and the policies supporting that purpose have driven the growth of the U.S. economy to its status of pre-eminence in the world. While some commentators may wish that pharmaceutical companies were motivated by the commentator’s own particular vision of the public good and by “pure” science, motivations of these sorts cannot produce the wealth of new drugs that are constantly coming onto the market, curing illnesses, preventing deaths and relieving suffering. Governmental regulations provide the framework of motivations and constraints within which companies must conduct their business and manage their affairs. One can scarcely blame a company for doing what it is supposed to be doing—namely, making products that are useful and that people (or their agents) are willing to pay for—within the constraints of law and regulation.

*Companies that gain financially from race-based studies should devote a large share of their profits to research aimed at uncovering underlying biological factors.*<sup>4</sup> Investigation of underlying biological factors is critically important to identifying more accurately those who will or will not benefit from the use of a particular drug; ultimately, most would agree that such research should be done. Who should do it, however, is a question that is best left to the mechanisms that are already in place to make such decisions: private companies guided by market factors and regulatory limits, and the public institutions that investigate fundamental biological questions, such as universities and the National Institutes of Health and other federal agencies. Institutions have been created to carry out basic research precisely because commercial companies do not and should not be expected to expend their

limited resources on research and development that will not, in their view, lead to commercially viable products.

## CONCLUSION

NitroMed and the FDA have been unjustly criticized for the way in which they have carried out their legal and moral obligations. Even when the facts underlying the criticisms are correct, they have often been evaluated in the context of a particular social vision or a personal sense of morality rather than in the context of the policies, laws and regulations that actually govern the way all companies, including drug companies, must function.

Most critics have responsibly recognized the overarching value of BiDil in saving and improving the lives of black patients with severe heart failure while noting important social factors—such as the historical mistreatment of blacks and contemporary healthcare disparities—that warrant caution and vigilance in designing and carrying out racially stratified RCTs. With that view, we could not agree more.

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