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BiDil: From Another Vantage Point

Despite criticisms of BiDil, its clinical benefits for African Americans have held up to scientific scrutiny.

by **Gary Puckrein**

ABSTRACT: In a recent *Health Affairs* Web Exclusive, Pamela Sankar and Jonathan Kahn argue against the Food and Drug Administration's approval of BiDil as a new drug for the treatment of heart failure in African Americans. Their paper questions the existence of disparities between African American and other heart-failure patients and the motivations of BiDil's developers and manufacturer. The disparities are confirmed and persistent, however, and BiDil's effectiveness is proven. If the authors' logic were to prevail, patients would be denied life-saving therapy. Continued investigation will likely narrow identification of patients who will benefit. [*Health Affairs* 25 (2006): w368–w374; 10.1377/hlthaff.25.w368]

HEALTH AFFAIRS RECENTLY PUBLISHED a pair of Web Exclusives on the controversy surrounding the Food and Drug Administration's (FDA's) approval of BiDil as a new drug for the treatment of heart failure in African Americans. In the first of those papers, Pamela Sankar and Jonathan Kahn argue against the development of the drug.¹ In an accompanying commentary, Rick Carlson provides some perspective on race and genetics, clarifying the general issues without addressing the logical and factual flaws in Sankar and Kahn's argument.²

Sankar and Kahn warn that BiDil “will cheat consumers—African Americans as well as everyone else. Furthermore, it threatens to set in motion a trend in the pharmaceutical industry for turning other widely used and cost-effective generics into patented, expensive drugs in the name of alleviating health disparities.” They further contend that the race-specific trial design and marketing of BiDil cannot be justified by any valid scientific analysis—that they were (and are) driven by patent law and market protection. The sum of their argument is that the original patent on BiDil was about to expire, so the patent holders cleverly managed to extend their exclusivity by alleging BiDil's value in treating African American heart-failure patients who were not being well served by existing medications. On the road to making this case, they propose to sweep away two decades of valuable clinical and epidemiological research.

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Recognizing Disparities

Sankar and Kahn rely on Kahn's previous work, published before FDA approval of BiDil, to make their case. In "How a Drug Becomes 'Ethnic,'" Kahn's core argument—where he questions verifiable data rather than theory or motivation—accuses BiDil's developers and NitroMed, its manufacturer, of "statistical mischief" (a concept elaborated at greater length in an even earlier article).³ He cites NitroMed's repeated assertion that "death rates from heart failure are more than twice as high in black patients than in white patients."⁴ (And it appears that NitroMed did overstate its case, neglecting to specify that this disparity is evident among younger patients but not among those age sixty-five and older.)

Kahn traces the origin of the 2:1 ratio in death rates back through a pair of studies published in 1999 to a 1987 editorial in the *American Heart Journal* by Richard Gillum.⁵ Gillum states that "the ratio of black-to-white rates was highest under age 65, approaching 1 in persons 75 years of age and over. For persons aged 35 to 74 years, the ratio of age-adjusted rates in blacks and whites was 1.8 for men and 2.4 for women." Kahn reports that Gillum's calculations were based on 1981 mortality rates, which would have been out of date in 1987, and he describes his own computation, based on more current data, of the ratio of deaths from heart disease for blacks and whites as "approximately 1.08:1." (He fails to report that his sources and methods also reveal the persistence of the disparity among younger patients: In 2002 the ratios were 1.71:1 for blacks and whites ages 35–74 and 2.54:1 for those ages 35–64.⁶ Aggregate mortality data from 1999 through 2002 indicate that nearly 17 percent of black heart-failure deaths were in the younger age [35–64] cohort, whereas only 5 percent of white heart-failure deaths were in this age cohort.⁷ In short, there are pronounced health disparities.)

After dismissing the disparities as products of commercial ambitions, Kahn challenges the consensus in the medical community that angiotensin-converting enzyme (ACE) inhibitors do not work as well in blacks as in whites. He cites studies that have failed to confirm the difference in response, but their findings have been insufficient to alter the medical consensus to date.⁸ (Citing recent studies, the American College of Cardiology/American Heart Association heart-failure guidelines summarize current understanding as follows: "Retrospective analysis of subgroup data has suggested that, as in the treatment of hypertension, black patients with [heart failure] may experience less efficacy than nonblacks from the use of [ACE inhibitors]. A recent analysis of a large [ACE-inhibitor heart-failure] trial that used a matched-cohort design confirmed that black patients had a greater number of hospitalizations for [heart failure] than matched white patients. However, rates of death in that trial were similar between black and non-black patients with [heart failure].")⁹

Having dismissed the disparities and any medical justification, Kahn comes to his eureka moment: There is essentially no clinical need for BiDil; the whole business is a fabrication driven by commercial interest. He also finds commercial moti-

vations in the development of BiDil as an “ethnic drug.” Sankar and Kahn repeat this argument in the wake of FDA approval of BiDil, but they do nothing to strengthen it.

Heart failure is a major problem for African Americans, which is likely to grow as the older proportion of the population increases in the coming years. Among men ages 45–64, the prevalence rates (per 100,000 population) for congestive heart failure are 5.97 for African Americans and 2.97 for Caucasians; among women in the same age group, the prevalence rates are 4.24 and 1.51, respectively.¹⁰ In that age group, African American men have a death rate that is 2.5 times higher than that of Caucasian men, and African American women have a death rate that is 2.7 times higher than that of Caucasian women.¹¹

These disparities have resisted advances in the standard treatment of heart failure, which has expanded in recent years from digoxin and diuretics to include ACE inhibitors/angiotensin II receptor blockers (ARBs), beta-blockers, and aldosterone antagonists. These drugs, particularly the ACE inhibitors, are not as effective in African Americans as in others. The difference is not well understood, but hypertension apparently plays an important role. NitroMed’s press releases overgeneralized the two-to-one mortality disparity, and this inaccuracy found its way into the popular press. It did not, however, contaminate the scientific literature or the FDA’s deliberations. The unexplained and untreated disparity in premature death between African American and other heart-failure patients added urgency to the development of BiDil and remains a source of both concern and scientific interest, but the effectiveness of BiDil is a separate issue. If there were no disparity in death rates, BiDil’s effectiveness would still justify its approval, although it would create a disparity to the disadvantage of whites.

Finding The Target

BiDil is a fixed-dose combination of two compounds: isosorbide dinitrate and hydralazine hydrochloride. Hydralazine hydrochloride is indicated, alone or as an adjunct, for hypertension. Isosorbide dinitrate is indicated for the prevention of angina pectoris due to coronary artery disease. Individually, neither drug is approved by the FDA for the treatment of chronic heart failure.

Starting in the 1980s, a series of trials was undertaken to determine the efficacy of using these two drugs in combination to treat heart failure. The Vasodilator-Heart Failure Trial (V-HeFT I) was the first trial organized to assess the long-term efficacy of using isosorbide dinitrate and hydralazine in combination as an adjunct to conventional therapy (at that time, digitalis and diuretics) for the treatment of heart failure. Physicians had started off-label experimentation with isosorbide dinitrate and hydralazine before V-HeFT I, but there was no prescribing information to guide their use of the medications. One of the goals of V-HeFT I was to provide prescribing guidelines. V-HeFT I suggested the efficacy of the therapy, but the standard was evolving.¹² After the completion of V-HeFT I, V-HeFT II was un-

dertaken to determine whether isosorbide dinitrate and hydralazine had an effect comparable to or different from that of enalapril, an ACE inhibitor that was rapidly becoming standard therapy for the treatment of heart failure.

The findings of V-HeFTs I and II, including a bioequivalence study, were presented to the FDA in the hope of winning approval for BiDil (the proprietary fixed-dose combination of isosorbide dinitrate and hydralazine) as a new drug for the treatment of heart failure. The FDA found that neither the drug combination used in V-HeFT I nor that used in V-HeFT II was bioequivalent to BiDil, and the combination did not outperform enalapril; it rejected the BiDil application.¹³ A retrospective analysis of the data from V-HeFTs I and II revealed something interesting, however: Patients who identified themselves as black appeared to respond better to the medication than those identified as white.¹⁴

NitroMed, in consultation with the FDA, designed a new trial to verify the combination's apparent effectiveness among African Americans. The African-American Heart Failure Trial (A-HeFT), which started in 2001, recruited heart-disease patients receiving standard treatment who identified themselves as African American. Half of the patients received BiDil in addition to the standard treatment; half received a placebo. The death rate among patients receiving BiDil fell so dramatically that the independent data and safety monitoring board recommended early termination of the trial. The group receiving BiDil showed a 43 percent improvement in survival.¹⁵

Sankar, Kahn, and others object to A-HeFT's design, particularly the absence of non-African American subjects. Oddly, they do not discount as unscientific clinical trials whose patient populations are all white or those in which minority populations are too small to represent meaningful samples. Troy Duster, another frequently cited critic, has observed: "The clinical trials for BiDil were conducted on only 1,050 African-Americans. No other groups were studied. Thus, the research had no case controls, the gold standard of scientific work in this field."¹⁶ He does not mention that the A-HeFT investigators, who designed the study in consultation with the FDA, had extracted adequate evidence from the V-HeFT studies to justify narrowing the focus to the most promising group. Even more curious, he seems to suggest that black patients who received standard therapy and a placebo instead of BiDil cannot be counted as a control group.

It could be argued that A-HeFT represents a rare instance of a trial that includes an adequate number of African American subjects. The FDA has promulgated guidelines for the collection and reporting of race and ethnicity data since 1998, but a recent study has found that almost half of the enrollees in studies supporting drug approvals between 1995 and 1999 were not identified by race.¹⁷ African Americans' participation averages below their proportion of the U.S. population, and Hispanic Americans participate at minuscule levels.

Lack of outreach appears to be a major cause for this underrepresentation in clinical trials.¹⁸ Underrepresentation of African Americans in clinical studies

might partially explain the development of a standard treatment for heart failure that has proved to be less effective for them. A larger study, including adequate representation of all minority groups, would have provided more comprehensive results than A-HeFT did and could have opened new doors for further exploration. However, as a more practical study, A-HeFT has proved the effectiveness of BiDil for African American patients.

Race, Medicine, And Commerce In The Twenty-First Century: Recognizing Priorities

Sankar, Kahn, and other critics of BiDil's approval as a race-based treatment have expressed concern about the medical and scientific validity of the concept of race. This concern is valid but, under present circumstances, impractical. Current research and medical practices recognize racial and other crude distinctions, in the absence of more precise information, every day. Citing the agency's recent approval of BiDil, the FDA's latest clinical-trials guidance captures the imperfect state of the art as follows:

Differences in response to medical products have already been observed in racially and ethnically distinct subgroups of the U.S. population. These differences may be attributable to intrinsic factors (e.g., genetics, metabolism, elimination), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors. For example, in the United States, Whites are more likely than persons of Asian and African heritage to have abnormally low levels of an important enzyme (CYP2D6) that metabolizes drugs belonging to a variety of therapeutic areas, such as antidepressants, antipsychotics, and beta blockers. Other studies have shown that Blacks respond poorly to several classes of antihypertensive agents (beta blockers and angiotensin converting enzyme...inhibitors). Racial differences in skin structure and physiology that can affect response to dermatologic and topically applied products have been noted. Clinical trials have demonstrated lower responses to interferon-alpha used in the treatment of hepatitis C among Blacks when compared with other racial subgroups [references omitted].¹⁹

Race may be the coarsest of discriminators, but it now has proven life-saving potential for heart-failure patients. The evidence that convinced the FDA predicts a dramatic increase in black patients' survival rate.

BiDil's Niche

The FDA's approval of BiDil as a heart-failure drug for "self-identified black patients" does not extend to the two compounds upon which BiDil is based. Sankar and Kahn are mistaken in asserting that there are "other widely used and cost-effective generics that can be substituted for BiDil." There is no FDA approval for the separate use of hydralazine and isosorbide dinitrate for heart failure.

In the United States, the FDA regulates trial and approval of new drugs as well as of generics that are equivalent to existing drugs. Before the FDA can approve a drug as a generic, the patent for the existing, or brand-name, drug must expire. The generic drug's maker must then demonstrate therapeutic equivalence to the brand-name drug. For BiDil, NitroMed submitted a New Drug Application (NDA), not an application for approval of a generic equivalent to a branded drug.

The FDA approved BiDil as a new drug for the treatment of heart failure in a

narrowly defined population. NitroMed has a patent for BiDil's use for treatment of heart failure and exclusivity for the combination. The FDA has found no generic combination to be bioequivalent to BiDil, and it recently confirmed that it has not approved any drug as therapeutically equivalent to BiDil and that it has not approved labeling for heart-failure treatment for either isosorbide dinitrate or hydralazine hydrochloride.²⁰ There will be no generic combination product available until the exclusivity expires.

Sankar, Kahn, and other critics find cause for skepticism in the commercial motivations of BiDil's developers. Their quarrel here is with the system that drives the development of pharmaceuticals and other medical treatments in the United States and internationally. The FDA depends on pioneering pharmaceutical companies to develop drugs, and these companies are profit-seeking enterprises. Without a financial incentive, pioneering companies would not invest their time and money in the development of BiDil or any other product.

A larger concern expressed by a number of critics is that BiDil, sometimes touted as representative of the trend toward "personalized medicine," is drawing attention and resources away from public concerns, including the economic, political, and social factors that contribute to health disparities. Both the drug's manufacturer and its critics advocate continued investigation into the genetic and other possible reasons for the difference in response to the drug, and both anticipate that the social concept of race will be superseded by more objective and precise criteria, narrowing the focus among African Americans to specific individuals who will benefit from the drug while also identifying non-African Americans who will benefit—probably on the basis of a genetic feature that is more common among African Americans than among other racial or ethnic groups.

Sankar and Kahn's criticisms focus on the drug's search for patients. A more important vantage point to consider is that of the patients who have been searching for an effective therapy.

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