BiDil for Heart Failure in Black Patients: Implications of the U.S. Food and Drug Administration Approval

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In 2005, the combination of hydralazine hydrochloride and isosorbide dinitrate was approved by the U.S. Food and Drug Administration (FDA) for treating heart failure in black patients. In departing from its long history of approving drugs for general clinical indications without regard to demographic classification, the FDA cited the need to address racial disparities in health as an important contributor to their decision. The authors argue that this decision, although perhaps well-intentioned, was based on flawed scientific interpretation of trial results that claimed differential drug response by race and ignored the considerable literature on the cause of racial disparities in health and health care. Because of its potential impact on future drug approvals, the FDA’s decision is a setback in the scientific and policy discourse on medical therapeutics and race and specifically hinders the efforts aimed at eliminating health and health care disparities.

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time, provide that scientific argument, but such data are not available in most cases. The recent case of bucindolol offers some important insights.

**Scientific Implications of the FDA Approval of BiDil**

The FDA approval of BiDil was based on the results of the African American Heart Failure Trial (A-HeFT) (11), a randomized, controlled trial of BiDil added to standard therapy for self-identified black patients with heart failure. The makers of BiDil had initially sought approval for the drug in the general patient population (not just in black patients) on the basis of results of earlier trials of the generic combination (12, 13), but approval was denied because of statistical concerns that the earlier trials had failed to account for the multiple end points analyzed (14). In addition, the earlier trials did not address the important question of whether the hydralazine hydrochloride–isosorbide dinitrate combination confers benefit when added to standard heart failure therapy (including angiotensin-converting enzyme [ACE] inhibitors and β-blockers). The A-HeFT evidence was clear—BiDil, when added to standard therapy, reduced mortality in black patients with advanced heart failure. Faced with this evidence, the FDA had 2 choices: approve BiDil for the general population—a practice consistent with years of previous drug applications—or approve BiDil only in black patients. In choosing the latter, the FDA chose the path with the most concerning scientific consequences both for heart failure treatments and for studies of medical therapies.

1. Drug approval for specific groups implies a differential drug response that has not been rigorously tested.

The FDA approval of BiDil in black patients implies that the treatment is efficacious only in black people and not in other racial groups. Although a 1999 post hoc subgroup analysis of 2 earlier hydralazine hydrochloride–isosorbide dinitrate trials in black and white patients (Veterans Administration Cooperative Vasodilator Heart Failure Trial [V-HeFT] I [12] and II [13]) suggested that the response to treatment may differ among races (15), the evidence is insufficient to base the current FDA decision. First, because the V-HeFT II investigators included enalapril as an active treatment comparison group, the subgroup analysis could not determine whether the observed racial difference was due to an increased response to hydralazine hydrochloride–isosorbide dinitrate or a decreased response to enalapril among black participants. Second, these older trials do not provide evidence for differential response to hydralazine hydrochloride–isosorbide dinitrate among contemporary patients who are receiving other standard heart failure therapies.

Finally, and perhaps most important, evidence from the subgroup analysis must be interpreted with the same caution as with other post hoc analyses of particular subgroups enrolled in clinical trials. Although such analyses are generally performed to determine whether response differs between groups, observed differences are far more likely to be in the degree of response (for example, “drug A is more efficacious in diabetics than nondiabetics”) than in the type of response (for example, “drug X is efficacious only in diabetics and not in nondiabetics”) (16). Reports of qualitatively different responses have not been consistently replicated and are particularly suspect when hypotheses have not been prespecified or appropriate adjustments have not been made for multiple hypothesis testing (16, 17) (which are both well-documented critiques of the analyses from V-HeFT I and II [1, 14]). Notably, the V-HeFT subgroup analysis did not prompt the major heart failure practice guidelines to recommended using these medications differently in black and white patients (18, 19).

In studying only black patients, the recent A-HeFT trial could not address the lack of treatment efficacy in other racial groups. However, because the approval of BiDil for black patients implies a lack of treatment efficacy in other race groups, the FDA decision has important clinical and scientific implications. Clinically, the use of this effective medication in other demographic groups is now technically “off-label” (a paradox for BiDil because the use of the generic combination as an alternative to standard therapy is approved for all individuals). Scientifically, racial differences in response to hydralazine hydrochloride–isosorbide dinitrate (and perhaps other heart failure medications) may now be thought of as “proven,” although the statistical interaction on which such a conclusion is based has not explicitly been tested. In addition, untested assumptions about differential responses by race generally lend credence to other untested assumptions, including heart failure as a different disease entity in black patients.

We should note that plausible biological mechanisms may explain a differential response of black patients to hydralazine hydrochloride–isosorbide nitrate, namely increased levels of nitric oxide in black people that are associated with adverse heart failure outcomes and may be reduced by hydralazine hydrochloride–isosorbide nitrate therapy (20). While such observations certainly merit further exploration, the association of a potential mediator of the differential drug response with a certain race group should not be the sole basis for drug approval exclusively in that race group.

Recent data on racial differences in drug response to another heart failure drug—bucindolol—offer an important lesson in this regard. The negative results of the randomized, controlled trial of bucindolol (the Beta-Blocker Evaluation of Survival Trial [BEST] [21]) are in stark contrast to those of several trials of other β-blockers that show mortality benefits in heart failure (22–24). The BEST authors speculated that the reason for their negative results may have been the substantial numbers of black participants in the trial and a decreased response to β-blocker therapy among them. In fact, subgroup analysis of the BEST results demonstrated a survival benefit among the...
nonblack participants that was not observed among the black participants. Recent genetic evidence suggests a biological mechanism for this difference because a polymorphism in the $\beta_1$-adrenergic receptor seems to be responsible for drug response. This polymorphism is more common in white patients (53%) than in black patients (38%), and when the genotypes are accounted for, the differences in drug response by race disappear (25, 26).

The bucindolol case highlights how genetic variation can lead to differences in treatment response but also that caution should be used when ascribing the differential response to race alone. Imagine that the FDA had approved bucindolol for treating only nonblack patients with heart failure on the basis of the BEST subgroup analysis. Such a decision would have resulted in the withholding of effective treatment from the 38% of black patients who have the polymorphism that is responsible for the drug response.

2. In approving a drug for a specific racial group, the FDA creates incentives for pursuing trials in less diverse patient populations.

Much has been written about the economic incentives of the makers of BiDil to secure FDA approval (14, 27–30). By signaling that the FDA would approve BiDil for an indication in black patients (1, 2), the FDA created a disincentive for the BiDil makers to pursue a larger, more expensive trial in a diverse patient population. Such a trial has a compelling rationale because the efficacy of hydralazine hydrochloride–isosorbide dinitrate added to standard therapy was not known for any patient population. Even by the drug manufacturer’s admission, BiDil will probably be efficacious in many nonblack patients with heart failure. Creating incentives for trials in single populations is counterproductive because these trials fail to yield important information about populations that are not tested (particularly if the consequence is an assumption of lack of efficacy in these populations), while also providing only limited information in the population of interest. Does BiDil work in black patients because they are black or because they are more likely to have another factor (such as prevalent hypertension) that might mediate the effect in all patients (31)? While larger trials allow for exploration of true mediators, smaller trials with limited variation make this more difficult.

3. In creating incentives for studies in less diverse patient populations, the FDA decision may lead to a diversion of resources away from studies of better therapeutics to those that support niche marketing.

Marketing to particular groups is a lucrative strategy for many products—from cars to soft drinks. Medications can also be profitably marketed to particular populations, especially treatments for conditions in which various therapies exist (for example, heart failure or AIDS) or treatments that may be one in a class of effective medications (for example, statins). Rather than being an aberration, BiDil may be the first of several medications that target a particular demographic group precisely because this is deemed to be the most lucrative marketing approach. Creating incentives for this strategy could lead to diversion of resources away from searching for better therapeutics to demonstrating efficacy in subgroups in the quest for niche markets. Although no one can fault drug companies for pursuing this strategy, the regulatory charge of the FDA should ensure that the approval process supports the highest scientific standards for the type of trials performed and the most accurate interpretation of trial results.

Policy Implications of the FDA Approval of BiDil

Despite the scientific limitations that are inherent in approving a drug for a single demographic group, the FDA found the argument—that BiDil would address racial disparities in health—compelling enough to depart from history. We argue that while the adverse scientific consequences of the decision are important, the setback in addressing racial disparities in health is also substantial.

1. By endorsing race as a treatment indication, the FDA unscientifically endorsed a biological model of race.

If A-HeFT included nonblack patients, such as self-identified white or Asian patients, and BiDil was found to be beneficial for self-identified black patients only, then current debate over the use of self-identified race as a proxy for biological, presumably genetic, differences would be useful (14, 32). However, as stated earlier, A-HeFT did not test for differential response by race to hydralazine hydrochloride–isosorbide dinitrate. Because the FDA had no clinical trial evidence on which to base its drug approval for a specific race, the approval is implicitly based on an assumed biological difference between black and nonblack patients. Self-identified race may be a reasonable proxy for genetic differences, and important biological differences may exist between black and nonblack patients. Certainly, there are reasonable arguments on both sides (33, 34). However, sidestepping the debate entirely and assuming a difference adds FDA regulatory imprimatur to one side of the argument without scientific evidence, thus diverting attention from a wide range of established causative or contributing factors that should continue to be addressed by investigators and policymakers.

2. The use of the health disparities argument to justify approval suggests a “solution” (race-targeted pharmacology) for a “problem” (racial disparities in health) and elevates biological difference in medication response to an important cause of health disparities without evidence.

Differential response to treatment certainly exists on the individual level and may exist on a population level as well, perhaps even among populations selected by self-identification of race (35). But evidence that differential response to treatment is an important contributor to health disparities is lacking. More black people die of heart failure than white people. This may reflect differences in mortality
rates among individuals with heart failure that have been observed in some (36) but not other (37, 38) studies. However, a major component of the high mortality rate from heart failure among black people is clearly the higher incidence of heart failure among them (18, 39, 40). Although the increased incidence of heart failure in black individuals has not been fully explained, it is likely predominantly due to inadequate treatment for heart failure risk factors, notably hypertension, and represents a known failing in our ability to equitably distribute efficacious treatments (18, 41, 42). In more general terms, by invoking the rhetoric for health disparities and applying it to the drug approval process when no direct evidence exists, while ignoring the evidence that health disparities are driven by disparities in health care and a wide range of social conditions, the FDA reframes the debate on addressing health disparities without scientific basis.

Reframing the debate has clinical consequences. For health care providers, who focus on the role of health care in influencing health disparities, the implicit message to focus on race-targeted medications conflicts with ample evidence documenting that the main health care–related racial disparity in cardiovascular disease is underutilization of standard therapies and procedures (43–46). Current evidence suggests that we should do more of the same, not more differently. Reframing health disparities as a pharmacologic phenomenon distorts existing evidence and may lead to less evidence-based care.

3. The use of health disparities to justify the “creation” of an expensive medication is perverse.

Of the social factors that contribute to disparities in health, poverty and income differentials are among the most important. While A-HeFT demonstrated that BiDil safely adds to the treatment for advanced heart failure, using the health disparities argument to justify the creation of an expensive “new” medication from 2 generic medications distorts the understanding of health disparities beyond recognition. BiDil costs about $1.80 per pill (47) or about 10 times as much as that of the generic combination. Considering the 3 times daily dosing of BiDil and the 4 times daily dosing of hydralazine hydrochloride–isosorbide dinitrate, the annual cost increase for BiDil is nearly $3000 per patient higher than that of the generic components. The ultimate effectiveness of BiDil both in treating real patients with heart failure and in combating racial disparities in heart failure outcomes requires recognition of this distorted economic reality.

**Conclusion**

In summary, the FDA decision to approve BiDil for treating heart failure in black patients is poor science and poor policymaking. Patients with heart failure deserve better.

**Authors’ Note:** Readers may be interested to know that the commercial response to BiDil has been mixed, apparently because of the resistance to increased pricing for generic products. While some states have included BiDil in their Medicaid formulary (such as Florida, California, and Michigan), other states have not. Variation among Medicare Part D plans and commercial insurers has been similar (48, 49).

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