

**BIDIL: A RACE-TARGETED DRUG FOR BLACK AMERICAN'S ONLY**

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**ABSTRACT**

It has been noted that pharma research toward race-targeted medicine and its criticism is going on simultaneously over the past few years. Some argued that drugs specifically target to cure particular racial groups could play a vital role against racial disparities in health. While others claimed that race-targeted medicine inappropriately treats race as a biological reason for racial disparities when broader social and environmental factors may offer better descriptions. Much of this debate includes the Food and Drug Administration's approval of drug BiDil in 2005, which became the first drug to be marketed for a specific racial group black Americans who suffers from heart failure (HF). This controversial drug was declared failed due to less attention of physician's as well as its high cost in market. The highlighted part of this review is that besides much criticism still this drug prescribed by majority of physicians. Moreover, BiDil is not only one which is race specific but also there are more drugs which have been claimed to have different effects in different racial or ethnic groups.

**Keywords:** Race, Black Americans, Food and Drug Administration, HF, BiDiL.© 2017 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2017.v10i11.20022>**INTRODUCTION**

The Centers for Disease Control and Prevention (CDC) latest report revealed that the pattern of life expectancy in the United States (U.S.) has actually been one of progressive improvement for all races of people since 1900 (Fig. 1). Their life expectancy at birth increased to 78.8 years in 2014 which was 70.8 years in 1970 (Fig. 1). For the white Americans, life expectancy raised by 10% (from 71.7 to 79.0 years) and 18% (from 64.1 to 75.6 years) for the black Americans. Among the significant race-sex groups, white women's continued to have the greatest life expectancy at birth (81.4 years), followed by black women (78.4 years), white men (76.7 years), as well as black men (72.5 years) (Fig. 2) [1].

The CDC report clearly indicates that white Americans could expect to live 3.4 years longer than black Americans under current mortality patterns, and this gap is due to higher death rate that includes heart disease, cancer, homicide, diabetes, and perinatal conditions.

Chronic diseases are the dominant contributors to the global burden of disease, and cardiovascular disease (CVD) is the largest contributor to worldwide disease which includes coronary heart disease (CHD) is a major cause of death and disability in developed countries [2]. Undoubtedly, CVD is the No. 1 killer of all Americans, and also stroke is the fourth-leading reason of fatality. Individuals of all ages, genders, races, and ethnic backgrounds are affected. Although treatments have actually progressed for coronary heart problem within the past two decades, black Americans continue to have double the risk of fatal coronary heart problem and remain more likely compared to whites to die from heart-related diseases (Fig. 3) [1,3].

In 2005, the U.S. Food and Drug Administration (FDA) approved BiDil drug to treat African-Americans with congestive HF. As it was approved due to the positive result seen in African-American Heart Failure Trial, but the drug was under controversy from the day of approval. The present review deals with the approval history of BiDil, its criticism, and the current status among physicians.

**RACE-TARGETED MEDICINE AND BIDIL**

Rates of in the US have consistently decreased since the 1970s for all races of people both death certificate data, and evidence suggest a

steeper decline in acute CHD mortality between 2000 and 2008 for whites than for blacks, widening a long-standing disparity [4]. Health disparities, as defined by the U.S. health-care system refers to population specific differences in the presence of disease, health outcomes, quality of health care, and access to health-care services that exist across racial and ethnic groups [5]. Due to these low health indicators, it would presume that minorities, specifically black Americans, would take actions to enhance their health. However, the opposite holds true. Black Americans are considered as distrustful of clinical research, which subsequently influences health results and quality of life. It has been reported [6] that black American community leaders capitalized on an opportunity to bring attention to black American health issues with respect to the drug BiDil, an HF drug. BiDil is connected to treat health-care disparities because it specifically targets the black American population who disproportionately struggle with heart disease. To reduce health disparities in racial populations, drug marketing research, is one mechanism. Advertising and marketing is an effective tool that not only advances the pharmaceutical drug's profit margin but also additionally educates the minority population on the benefits of seeking treatment. Race-targeted medication is extremely debated and noted as a result of such targeted race medication may advance the treatment process at one hand, however, on the other hand, it may negatively uphold stereotypes and ideologies of certain groups.

**CONTROVERSIAL HISTORY OF BIDIL AND ITS FDA APPROVAL**

The drug BiDil, a combination of two generic medications - hydralazine hydrochloride and isosorbide dinitrate (hydralazine/ISDN, Fig. 4) in a single tablet, has an appealing past despite its favorable results in the black American community. BiDil was patented by cardiologists Jay Cohn and Peter Carson in 1989 for congestive HF. The initial study of BiDil failed to receive the FDA approval. The first FDA application was submitted in 1997, however, the results failed to show enough statistical efficacy for a multiracial population with CVD. On the recommendation of members of FDA's advisory committee, NitroMed pharmaceuticals reexamined the clinical trial data along racial lines.

Under the trial [7], a total of 1,050 men and women, who self-identified as black Americans, were enrolled with the New York Heart Association over 85% class III HF at 169 centers in the US. All black patients had

stable symptomatic cardiac arrest. They were needed to have left ventricular ejection fraction (LVEF)  $\leq 35\%$  or left ventricular internal diastolic dimension  $>2.9 \text{ cm/m}^2$  plus LVEF  $<45\%$ . These individuals

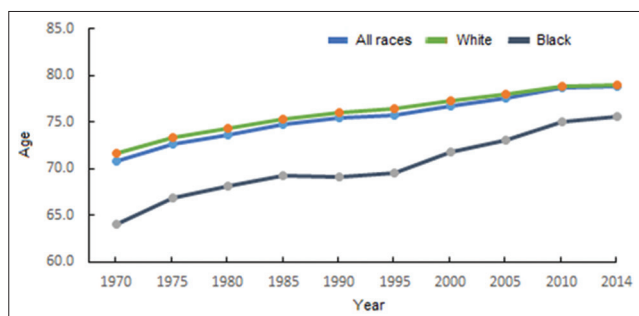


Fig. 1: Life expectancy, by race: United States, 1970-2014. Source: Centers for Disease Control and Prevention

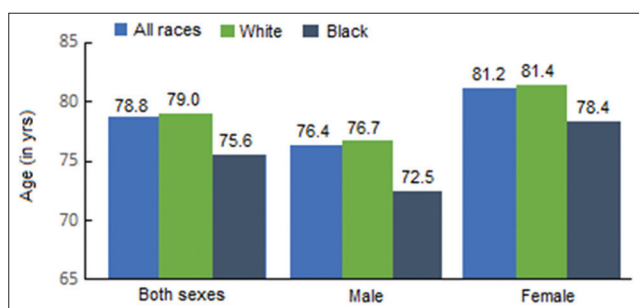


Fig. 2: Life expectancy at birth, by race, and sex: United States. Source: Centers for Disease Control and Prevention

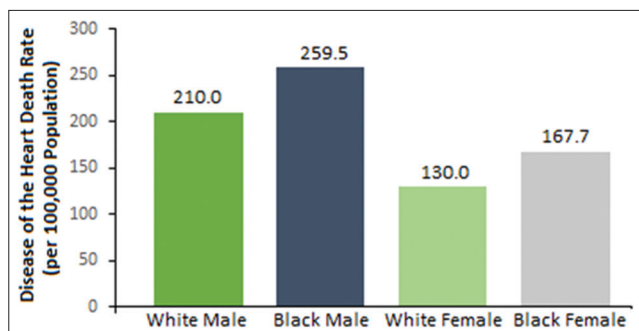


Fig. 3: Heart diseases death rate, by race, and sex: United States. Source: Centers for Disease Control and Prevention

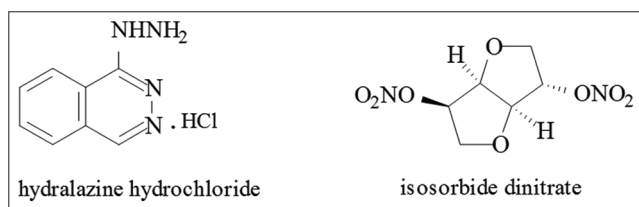


Fig. 4: BiDil, combination of two generic medications

were maintained on stable background therapy and randomized to BiDil (n=518) or placebo (n=532). They were treated for up to 18 months initiated with three doses of BiDil (hydralazine [37.5 mg]/ISDN [20 mg]) daily and titrated to a target dose of (75/40) mg three times daily or to the maximum tolerated dose. In the randomized population, with a mean age of 57 years was 60% of male having 1% NYHA class II, 95% NYHA class III, and 4% NYHA class IV. They were generally treated with standard therapy for HF including diuretics (94%),  $\beta$ -blockers (87%), angiotensin-converting enzyme inhibitors (ACE-I; 78%), angiotensin II receptor blockers (ARBs; 28%), either ACE-I or ARB (93%), digitalis glycosides (62%), and aldosterone antagonists (39%) [6].

The primary end point was a composite score consisting of all-cause mortality and first hospitalization for HF. The trial was ended early to avoid additional deaths among patients receiving a placebo. With a median follow-up of 12 months, fixed dose of BiDil showed statistically significant 43% reduction in all-cause mortality ( $p=0.012$ , Table 1) [7]. The primary end point also showed a significant effect toward BiDil ( $p\leq 0.021$ , Table 1) and also decreased the number of hospitalizations by 39% as well as length of hospital stay compared with standard therapy alone for HF ( $p<0.001$ ; Table 1) [8].

**CRITICISMS OF BIDIL**

It was not surprised that approval of BiDil, specifically for black Americans led to dialogs in both the scientific and biomedical fields. Critics augmented that a drug only for blacks would prevent its use in other individuals who might benefit, and that race is at best a crude marker for underlying hereditary and physical variations [9]. An editorial on racial profiling in medicine pointed that “race is a social construct, not a scientific classification. After 400 years of social disruption, geographic dispersion, and genetic intermingling, there are no alleles that define the black people of North America as a unique population or race [10].” The drug was criticized politically, commercially, and scientifically.

In the political fields, the FDA is criticized for approving the drug BiDil because the drug is targeted for a specific population, black Americans. Historically, the FDA has discouraged clinical research practices that take advantage of marginalized groups. It is argued that the FDA’s decision “may be a setback to scientific discourse on therapeutics and may be specifically deleterious to efforts aimed at addressing disparities in health and health care [11]. BiDil has further been criticized for exploiting the black American community for corporate profit and to a poor precedent of racial segregation in medicine [6]. Even more, the drug was marketed as a race-specific treatment, but in reality, there was evidence that the drug was effective across racial lines [12].

Commercially, the drug also criticized for its price because the generic drug was priced significantly lower at approximately \$1.50-\$3.00 while BiDil was priced at \$5.40-\$10.80 per day for the treatment. It would seem that if the goal were to increase access to health care and decrease disparities in the provision of health, the drug manufacturer would have priced the drug in a range that was affordable for the population. Despite the discounts and gratuitous availability of the drug for certain groups, cardiologists argued that the drug cost exceeded many patients’ financial ability to pay [13]. However, accounting for insurance and other factors it is arguable whether the cost of the drug is commercially exploiting the black American population. BiDil was not only the single drug which has shown better

Table 1: Results of A-HeFT (intent-to-treat population)

End point	BiDil group (n=518)	Placebo group (n=532)	Hazard ratio (95% CI)	Risk reduction
Composite score	-0.16±1.93	-0.47±2.04	-	0.021
Death from any cause	6.20%	10.20%	0.57 (0.37-0.89)	43% (p=0.012)
First hospitalized for heart failure	16.40%	24.40%	0.61 (0.46-0.80)	39% (p<0.012)

CI: Confidence interval, A-HeFT: African-American Heart Failure Trial

response to a specific race people. There are many medicines or their combinations have been also claimed to have differences in either safety or, more commonly, efficacy among racial or ethnic groups. However, these claims are universally controversial [10,14,15], and there is no general opinion on how important race or ethnicity is in determining drug response [16]. There is a compilation of drugs (Table 2) to have different effects in different racial or ethnic groups on for an overview of the relationship between racial or ethnic on the basis of literature [17].

There are literatures available which reveal that several combination products have shown to be effective in the treatment of type 2 diabetes also [52]. Glucovance is an example of a combination of glyburide and metformin which was proven to reduce fasting plasma glucose by 50-60 mg/dl. Other combinations include Metaglip (glipizide/metformin) and Avandamet (rosiglitazone/metformin and Duetact (pioglitazone/glimepiride) [53-55].

**CURRENT STATUS OF BIDIL AMONG PHYSICIAN'S**

The guidelines of the American College of Cardiology as well as the American Heart Association and Heart Failure Society of America recommending BiDil to self-identified black Americans. This drug could be prescribed by the physician's to black Americans, as a complement to the standard therapy, for the treatment of HF, to improve their survival, length of time to hospitalization, and improve patient-reported functional status [56,57]. However, the drug BiDil is underutilized by the physician's and prescribed to less than 20% of black Americans [58]. Further, it has been noted that individual adherence to this regimen is generally poor because of regular negative responses, including migraine, dizziness, and gastrointestinal problems along with the large number of tablets individuals have to take [8,9,57].

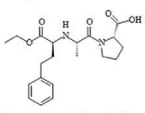
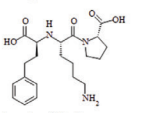
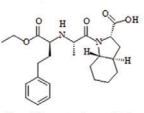
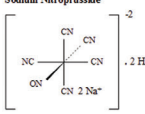
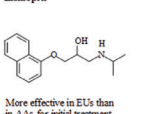
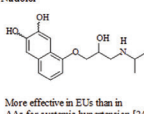
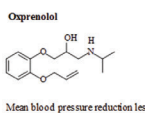
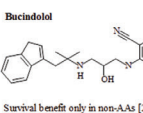
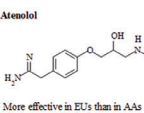
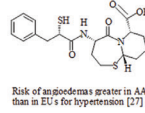
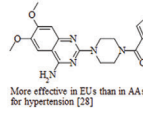
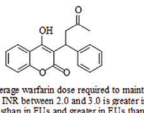
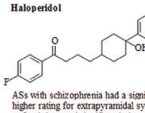
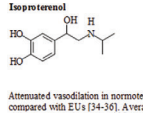
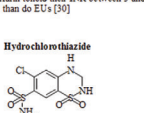
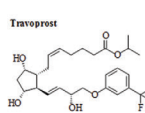
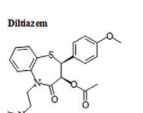
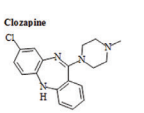
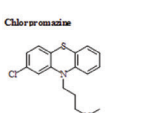
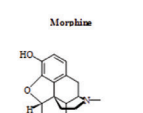
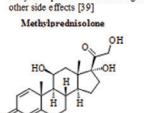
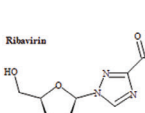
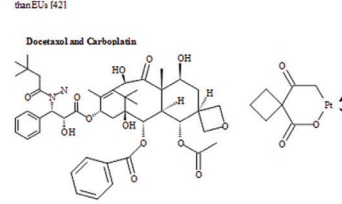
Beside all the controversies, the drug BiDil is still existing in the market and recommended by physician's. A recent study [59] presents an analysis of the factors influencing prescription of BiDil by physician's and investigated whether exposure to the controversies behind the drug has an impact on their therapeutic judgments. Study based on the two groups of physician's where one group receiving information about the controversy over BiDil. The outcome of the study reveals that 27% of the medical professionals are using individual's race as a major factor in making treatment decisions. While, 33% reported the ineffectiveness of standard treatments, 25% the seriousness of the disease, and 15% other undefined factors as a primary determining criteria in recommending BiDil. On the other hand, 68% of physician's reported that they were not familiar with any controversy surrounding BiDil. In general, physicians are recommending BiDil drug and want to recommend more to black patients compare to white-patients.

**CONCLUSION**

Having strong clinical trial proofs as well as basic scientific information clearly indicates the benefits of BiDil are in favor of self-identified black patients but still the proper utilization of the drug remains poor. There is a need of collective efforts by the scientific community, physician's, and public health officials for the better future of the BiDil. They should recognize and execute strategies to overcome patient and service provider barriers to appropriate evidence-based care for HF, specifically in black Americans, to conquer unacceptable disparities in HF morbidity and also mortality.

The discovery of BiDil is a sign of hope to resolve possible racial differences in clinical response to medicines and narrowing the unequal access to clinical services. The development of race-targeted medicines highlights potentially distinctive clinical demands in a racial community. Due to the historical injustices surrounding black Americans and scientific research, the development of BiDil needs to be considered as not only a drug development but also as a socially progressive step that could raise minority involvement in research.

**Table 2: Response of drugs to different racial or ethnic groups**

<p><b>Enalapril</b></p>  <p>Less response in AAs in EUs with left ventricular dysfunction [18]</p>	<p><b>Lisinopril</b></p>  <p>Lowering of Blood pressure in EUs but not in AAs [19]</p>	<p><b>Trandolapril</b></p>  <p>AAs with hypertension required 2 to 4 times greater dose to obtain similar lowering of blood pressure to EUs [20]</p>
<p><b>Sodium Nitroprusside</b></p>  <p>Attenuated vasodilation response to methacholine and sodium nitroprusside in normotensive AAs compared with EUs [21,22]</p>	<p><b>Lisinopril</b></p>  <p>More effective in EUs than in AAs for initial treatment of hypertension [23]</p>	<p><b>Nadolol</b></p>  <p>More effective in EUs than in AAs for systemic hypertension [24]</p>
<p><b>Oxprenolol</b></p>  <p>Mean blood pressure reduction less for AAs than for EUs [25]</p>	<p><b>Bucindolol</b></p>  <p>Survival benefit only in non-AAs [26]</p>	<p><b>Atenolol</b></p>  <p>More effective in EUs than in AAs for hypertension [27]</p>
<p><b>Omapatrilat</b></p>  <p>Risk of angioedema greater in AAs than in EUs for hypertension [27]</p>	<p><b>Prazosin</b></p>  <p>More effective in EUs than in AAs for hypertension [28]</p>	<p><b>Warfarin</b></p>  <p>Average warfarin dose required to maintain the INR between 2.0 and 3.0 is greater in AC than in EUs and greater in EUs than in AAs [29]. ACs and Indo-As require more warfarin to hold their INR between 3 and 4.3 than do EUs [30]</p>
<p><b>Haloperidol</b></p>  <p>As with schizophrenia had a significantly higher rating for extrapyramidal symptoms at fixed dose and significantly lower mean required dose than did EUs [31]. Extrapyramidal side effects higher in Chinese than non-Chinese individuals [33]</p>	<p><b>Isoproterenol</b></p>  <p>Attenuated vasodilation in normotensive AAs compared with EUs [34-36]. Average dose giving heart rate increase of 25 beats per min is more than 2 times higher in AAs than in EUs [37]</p>	<p><b>Hydrochlorothiazide</b></p>  <p>Greater systolic and diastolic blood pressure responses in AAs than in EUs [31]</p>
<p><b>Tavoprost</b></p>  <p>Response greater in AAs than in EUs for ocular hypertension [38]</p>	<p><b>Diltiazem</b></p>  <p>More effective in AAs than in EUs for hypertension [39]</p>	<p><b>Clozapine</b></p>  <p>AsAs showed a greater change than EUs in total scores of the 8-item Brief Psychiatric Rating Scale while receiving a significantly lower mean dose of Clozapine and were significantly more likely to experience anticholinergic and other side effects [39]</p>
<p><b>Chlorpromazine</b></p>  <p>EUs received significantly larger maintenance doses than did either AAs or HIs [40]</p>	<p><b>Morphine</b></p>  <p>Reduction in blood pressure was greater in EUs than in Chinese [41]. AAs more susceptible to depression of respiratory response than EUs [42]</p>	<p><b>Methoprednisolone</b></p>  <p>Adverse effects (steroid-associated diabetes) more common in AAs than in EUs [43]</p>
<p><b>Ribavirin</b></p>  <p>AAs have lower rate of response to treatment than do EUs [44]</p>	<p><b>Docetaxel and Carboplatin</b></p>  <p>Greater response in AAs than in EUs with advanced non-small cell lung cancer [45]</p>	
<p><b>Interferon</b></p> <p>Poorer response in AAs than in EUs [46,47]</p>	<p><b>Danaparoid</b></p> <p>Significantly more EUs than AAs had favorable outcome at 3 months (for ischemic strokes) [28]</p>	<p><b>Insulin</b></p> <p>Insulin sensitivity significantly lower in HIs and AAs than in EUs, and greater acute insulin response in AAs than in HIs [48]</p>
<p><b>6-MP, Methotrexate and other ALL agents</b></p> <p>Significant difference in response by ethnicity for childhood ALL: AAs &gt; EUs &gt; HIs &gt; AAs [49]. EUs have better survival than do AAs and HIs [50]. AAs, HI and AI children with ALL have worse survival than do EUs and AS/PI children [51]</p>		

Racial or ethnic groups: AA: African American, AC: Afro-Caribbean, AI: American Indian and Alaskan Native, AS: Asian, EU: European ancestry, HI: Hispanic, PI: Pacific Islander, ALL: Acute lymphoblastic leukemia, INR: International Normalized Ratio (for blood clotting time)

Scientifically, there are widespread criticisms to the use of race-targeted medicine; the more important question to explore is whether race-based medicine can reduce health disparities. Medical research should



by no means perpetuate stereotypes and racism, but if race-targeted medicine can close the gap in the health indicators that relate to access to care, perhaps race-based medicine is a solution and not an actual problem.

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