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

Kirsten Bibbins-Domingo, PhD, MD, and Alicia Fernandez, MD

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.

Ann Intern Med. 2007;146:52-56. www.annals.org
For author affiliations, see end of text.

In 2005, the U.S. Food and Drug Administration (FDA) approved BiDil (NitroMed, Lexington, Massachusetts), a combination of 2 generic medications—hydralazine hydrochloride and isosorbide dinitrate—in a single tablet, for treating heart failure in black patients. BiDil was approved for a specific racial group—which is a first for the FDA and is a clear departure from the FDA's long history of approving treatments for clinical conditions regardless of demographic classification (with the occasional exception of sex). One rationale for this departure was that the drug approval was important for addressing racial disparities in health (1–3). We argue that the FDA decision, although perhaps well-intentioned, 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.

Clinical Trials and Drug Approval

Because many patient characteristics can influence variability in drug response, randomized, controlled trials have attempted to include a broad spectrum of the patient population, an approach specifically endorsed by the National Institutes of Health policy on the inclusion of women and minorities (4). Including a broad patient population assures that most information on variations in drug efficacy is available for patients who are affected by the same condition. It also allows for investigators to research explanatory factors that may underlie variability, from simple descriptions (for example, "drug A is less effective in older individuals") to more complex explanations (for example, "the lower efficacy of drug A in older individuals is partially explained by a higher burden of coronary disease").

The merits of including broad patient populations in randomized, controlled trials are most clearly seen in studies in which this practice has not occurred, such as the trials of aspirin for the primary prevention of coronary disease. Although earlier trials—almost exclusively in men—demonstrated the efficacy of aspirin (5–7), a recent trial in women did not show this benefit (8). Were the observed differences because of fundamental physiologic differences between men and women in their manifestation of coronary disease and their response to aspirin or because of the consequences of specific features of the trials (such as distinct dosing regimens, variations in inclusion criteria, or advances in other adjunctive therapies)? A trial that had included adequate numbers of both men and women would have answered many lingering questions despite data from well-done trials done in each population separately.

In the past, trials have restricted enrollment to specific demographic groups. The African American Study of Kidney Disease and Hypertension (AASK) trial (9, 10) is a recent prominent example. This randomized, controlled trial of different antihypertensive treatments for hypertensive nephrosclerosis included only black participants. Black people are disproportionately affected by hypertension and kidney disease, and arguments both for efficiency and equity underlie the decision to explore treatments in this understudied patient population. However, the AASK investigators did not claim a race-specific effect of these therapies and reported instead on the general treatment effects for hypertensive nephrosclerosis (9, 10). A fundamental consistency in human biological responses is assumed in this type of trial reporting and in the FDA drug approval process, which has for years based approval of therapeutics for the general population on evidence from trials in mostly white, mostly male patient populations. Drugs are approved for treating clinical entities, not for treating specific demographic subgroups. Departures from this logic should require a compelling scientific argument with clear evidence of the biological mechanism underlying the differential response. Pharmacogenomic advances may, over

See also:

Print
Related article 57

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 β_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 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).

From the University of California, San Francisco, San Francisco, California.

Acknowledgments: The authors thank the organizers and participants of the special symposium on the implications of BiDil at the 2005 Society of General Internal Medicine Annual Meeting, New Orleans, Louisiana, 11-14 May 2005, including Drs. Giselle Corbie-Smith, Carol Horowitz, Valerie Stone, Christopher Phillips, and Jack Geiger.

Grant Support: Dr. Bibbins-Domingo is supported by grants from the Robert Wood Johnson Foundation (Amos Medical Faculty Development award) and the National Heart, Lung, and Blood Institute (contract no. N01-HC-95095), and Dr. Fernandez is supported by a K23 award from the National Center for Research Resources of the National Institutes of Health (K23 RR01832401).

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Kirsten Bibbins-Domingo, PhD, MD, Division of General Internal Medicine, San Francisco General Hospital, University of California, San Francisco, Box 1364, San Francisco, CA 94143-1364; e-mail, bibbinsk@medicine.ucsf.edu.

Current author addresses are available at www.annals.org.

References

1. **Nissen SE.** Report from the Cardiovascular and Renal Drugs Advisory Committee: US Food and Drug Administration; June 15–16, 2005; Gaithersburg, Md. Circulation. 2005;112:2043-6. [PMID: 16186439]
2. Summary minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting for June 16, 2005. Rockville, MD: U.S. Food and Drug Administration, Center for Drug Evaluation and Research; 2005. Accessed at www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4145M2.pdf on 25 October 2006.
3. **Saul S.** F.D.A. panel approves heart remedy for blacks. NY Times (Print). 2005:C4. [PMID: 15981396]
4. Inclusion of women and minorities as participants in research involving human subjects: policy implementation page. Bethesda, MD: National Institutes of Health, Office of Extramural Research; 2005. Accessed at http://grants.nih.gov/grants/funding/women_min/women_min.htm on 2 November 2006.
5. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med. 1989;321:129-35. [PMID: 2664509]
6. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. Lancet. 1998;351:233-41. [PMID: 9457092]
7. **Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, et al.** Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed). 1988;296:313-6. [PMID: 3125882]
8. **Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al.** A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352:1293-304. [PMID: 15753114]
9. **Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, et al.** Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA. 2001;285:2719-28. [PMID: 11386927]
10. **Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et**

al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002; 288:2421-31. [PMID: 12435255]

11. **Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, et al.** Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351:2049-57. [PMID: 15533851]

12. **Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al.** Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986;314:1547-52. [PMID: 3520315]

13. **Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al.** A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med. 1991;325:303-10. [PMID: 2057035]

14. **Sankar P, Kahn J.** BiDil: race medicine or race marketing? Health Aff (Millwood). 2005;Oct 11. [Epub ahead of print]. [PMID: 16219647]

15. **Carson P, Ziesche S, Johnson G, Cohn JN.** Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. J Card Fail. 1999;5:178-87. [PMID: 10496190]

16. **Yusuf S, Wittes J, Probstfield J, Tyroler HA.** Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. JAMA. 1991;266:93-8. [PMID: 2046134]

17. **Pocock SJ, Hughes MD, Lee RJ.** Statistical problems in the reporting of clinical trials. A survey of three medical journals. N Engl J Med. 1987;317:426-32. [PMID: 3614286]

18. **Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al.** ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation. 2005;112: e154-235. [PMID: 16160202]

19. **Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al.** ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. Circulation. 2001;104:2996-3007. [PMID: 11739319]

20. **Kalinowski L, Dobrucki IT, Malinski T.** Race-specific differences in endothelial function: predisposition of African Americans to vascular diseases. Circulation. 2004;109:2511-7. [PMID: 15159296]

21. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344:1659-67. [PMID: 11386264]

22. **Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al.** Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344:1651-8. [PMID: 11386263]

23. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation. 1994;90:1765-73. [PMID: 7923660]

24. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353:2001-7. [PMID: 10376614]

25. **Liggett SB, Mialet-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, et al.** A polymorphism within a conserved beta(1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. Proc Natl Acad Sci U S A. 2006;103:11288-93. [PMID: 16844790]

26. **Nainggolan L.** First genetically targeted drug for heart disease? HeartWire. 2006;11 July. Accessed at www.theheart.org on 25 October 2006.

27. **Kahn J.** How a drug becomes "ethnic": law, commerce, and the production of racial categories in medicine. Yale J Health Policy Law Ethics. 2004;4:1-46. [PMID: 15052858]

28. **Kahn J.** "Ethnic drugs." Hastings Cent Rep. 2005;35:1 p following 48. [PMID: 15799501]

29. **Kahn J.** Misreading race and genomics after BiDil [Letter]. Nat Genet. 2005; 37:655-6. [PMID: 15990879]

30. **Kahn JD.** Pharmacogenetics and ethnically targeted therapies: racial drugs need to be put in context [Letter]. BMJ. 2005;330:1508; author reply 1508. [PMID: 15976430]

31. **Moran AE, Cooper RS.** Isosorbide dinitrate and hydralazine in blacks with heart failure [Letter]. N Engl J Med. 2005;352:1041-3; author reply 1041-3. [PMID: 15758018]

32. **Carlson RJ.** The case of BiDil: a policy commentary on race and genetics. Health Aff (Millwood). 2005;Oct 11. [Epub ahead of print]. [PMID: 16219648]

33. **Burchard EG, Ziv E, Coyle N, Gomez SL, Tang H, Karter AJ, et al.** The importance of race and ethnic background in biomedical research and clinical practice. N Engl J Med. 2003;348:1170-5. [PMID: 12646676]

34. **Sankar P, Cho MK, Condit CM, Hunt LM, Koenig B, Marshall P, et al.** Genetic research and health disparities. JAMA. 2004;291:2985-9. [PMID: 15213210]

35. **Sehgal AR.** Overlap between whites and blacks in response to antihypertensive drugs. Hypertension. 2004;43:566-72. [PMID: 14757779]

36. **Dries DL, Exner DV, Gersh BJ, Cooper HA, Carson PE, Domanski MJ.** Racial differences in the outcome of left ventricular dysfunction. N Engl J Med. 1999;340:609-16. [PMID: 10029645]

37. **Rathore SS, Foody JM, Wang Y, Smith GL, Herrin J, Masoudi FA, et al.** Race, quality of care, and outcomes of elderly patients hospitalized with heart failure. JAMA. 2003;289:2517-24. [PMID: 12759323]

38. **Mathew J, Wittes J, McSherry F, Williford W, Garg R, Probstfield J, et al.** Racial differences in outcome and treatment effect in congestive heart failure. Am Heart J. 2005;150:968-76. [PMID: 16290973]

39. **Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al.** Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2006;113:e85-151. [PMID: 16407573]

40. **Kahn J.** Getting the numbers right: statistical mischief and racial profiling in heart failure research. Perspect Biol Med. 2003;46:473-83. [PMID: 14593217]

41. **Hertz RP, Unger AN, Cornell JA, Saunders E.** Racial disparities in hypertension prevalence, awareness, and management. Arch Intern Med. 2005;165: 2098-104. [PMID: 16216999]

42. **Alexander M, Grumbach K, Selby J, Brown AF, Washington E.** Hospitalization for congestive heart failure. Explaining racial differences. JAMA. 1995; 274:1037-42. [PMID: 7563454]

43. **Barnato AE, Lucas FL, Staiger D, Wennberg DE, Chandra A.** Hospital-level racial disparities in acute myocardial infarction treatment and outcomes. Med Care. 2005;43:308-19. [PMID: 15778634]

44. **Lillie-Blanton M, Maddox TM, Rushing O, Mensah GA.** Disparities in cardiac care: rising to the challenge of Healthy People 2010. J Am Coll Cardiol. 2004;44:503-8. [PMID: 15358011]

45. **Schneider EC, Leape LL, Weissman JS, Piana RN, Gatsonis C, Epstein AM.** Racial differences in cardiac revascularization rates: does "overuse" explain higher rates among white patients? Ann Intern Med. 2001;135:328-37. [PMID: 11529696]

46. **Trivedi AN, Zaslavsky AM, Schneider EC, Ayanian JZ.** Trends in the quality of care and racial disparities in Medicare managed care. N Engl J Med. 2005;353:692-700. [PMID: 16107622]

47. **Saul S.** Maker of heart drug intended for blacks bases price on patients' wealth. NY Times (Print). 2005:C3. [PMID: 16060015]

48. **Saul S.** 2 officials quit amid slow sales of heart drug for blacks. The New York Times. 22 March 2006.

49. **Brooks J.** Where's the BiDil? Hattiesburg American. 18 July 2006.

Current Author Addresses: Drs. Bibbins-Domingo and Fernandez: Division of General Internal Medicine, San Francisco General Hospital, University of California, San Francisco, Box 1364, San Francisco, CA 94143-1364.