

# The Use of Race and Ethnicity in Medicine: Lessons from the African-American Heart Failure Trial

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The practice of using race or ethnic origin as a distinguishing feature of populations or individuals seeking health care is a universal and well-accepted custom in medicine. Although the origin of this practice may, in part, reflect past prejudicial attitudes, its use today can certainly be defended as a useful means of improving diagnostic and therapeutic efforts. Indeed, the tradition of dividing populations by some racial distinction in clinical research has nearly always revealed differences in mechanisms of disease and disease frequency that can enhance diagnostic and therapeutic precision.

At the conference occasioning this symposium, Professors Duster and Rotimi provided persuasive evidence that so-called race is not an accurate way to distinguish populations and that identification by race has led to serious prejudice.<sup>1</sup> Professor Cho pleaded that race should never be used to characterize population differences.<sup>2</sup> When I reminded her of the powerful evidence that diseases do show different prevalence and treatment responsiveness in populations defined by race, and remarked that I was concerned about “throwing out the baby with the bathwater,” Professor Cho replied that there is no “baby,” as she argues in this symposium. But the “baby” does exist. There does appear to be important differences in disease and therapeutic response among populations defined by race.

Since the practice of medicine is heavily and appropriately influenced by statistical likelihood, it is important for health care providers to know that it is not cost-effective to search for sickle cell disease in a white anemic patient or to search for cystic fibrosis in a black patient with lung disease. These observed racial differences in disease frequency may be genetically, rather than racially or geographically determined, but in the absence of more refined technology, the racial designation, crude as it is, serves as a useful and available surrogate.

The fact that black hypertensive patients respond on average less well than white patients to treatment with an angiotensin converting enzyme (ACE) inhibitor<sup>3</sup> may be genetically or environmentally determined, and this difference does not exclude an excellent response in some black patients and a poor response in some white patients. Nonetheless, the knowledge of this difference in likelihood of response may appropriately be used by a health care provider in selecting a

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drug or a dose of a drug with which to initiate therapy in a given patient.

The debate, therefore, should not be over the existence of population differences, but how to describe those differences with more precision. Those who argue against our current approach may wish that differences did not exist, but they do. They are identified by statistical differences among definable populations in prevalence and physiological mechanisms. These population differences cannot in the first instance be classified as genetic, geographic, or environmental. They are observed differences in populations identified by a variety of demographic criteria. Railing against what some claim are misguided efforts to use racial, ethnic, or geographic distinctions does not make the differences disappear. We should be working toward better approaches in dealing with the differences, not raising legal and moral arguments, as Professor Roberts has,<sup>4</sup> claiming that any effort at distinction is wrong.

Clinical trials utilize a variety of demographic and physiological variables to select patients for optimal risk or therapeutic response. It is important to consider how race compares with other determinants of this risk and response. Race, by whatever method is used for designation, is a continuous variable with, at best, arbitrary distinctions. Other demographic variables also are continuous. An age range often is employed as an entrance criterion for a clinical trial. The eligibility age range discriminates against those outside this range even though they may individually be at similar risk and response as those within the range. No one raises the age discrimination issue, and a positive trial may make a therapy available for all ages, regardless of the trial's entrance criteria.

Similarly, hypertension, hyperlipidemia, and diabetes represent arbitrary categorization of individuals' blood pressure, cholesterol, and blood sugar levels, which are actually continuous variables.<sup>5</sup> In practicing medicine and performing clinical trials, these arbitrary categorizations are used to identify patients at higher risk and greater likelihood of therapeutic response. Those not meeting these criteria are excluded from a clinical trial, even though their risk and response to treatment may be similar. Even such disease states as "coronary artery disease" and "left ventricular dysfunction," which often serve as entrance criteria for studies, are continuous variables not easy to categorize. Coronary artery disease develops over years. At what point do we designate it as "present?" Left ventricular dysfunction, if assessed by the usual criterion of "ejection fraction," is a continuous variable. At what level is it appropriately labeled as "abnormal?" The selection of arbitrary criteria for

entrance into a trial is based on many factors, including statistical likelihood of a favorable response, but these entrance characteristics should not necessarily confine use of an effective therapy to individuals with such arbitrarily selected variables. The establishment of entrance criteria for a trial, therefore, does not dictate who should be treated in practice. The judgment of the health care provider in extrapolating from the trial to clinical practice is essential. This judgment should be based on insights regarding the mechanism of the treatment effect and the importance of the arbitrary entrance criteria. When racial or ethnic distinctions are used as eligibility criteria, the same need for insight and judgment is required.

The African-American Heart Failure Trial (A-HeFT) was carried out in a population that showed a remarkably favorable and life-saving response to the drug BiDil.<sup>6</sup> The choice to study a population self-identifying as African-American was based on a wealth of prior scientific data. Those data showed a higher prevalence in that population than in a self-identified white population of certain phenotype characteristics:

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hypertension, salt sensitivity, nitric oxide deficiency, low renin activity, and more severe vascular disease.<sup>7</sup> These differences may reflect genetic or environmental contributions, most likely a combination of both. More importantly, a prior study had demonstrated a striking difference in apparent response to the BiDil drug combination in patients self-identified as African-American versus white.<sup>8</sup> The benefit of BiDil ultimately shown in the A-HeFT Trial was so profound that it would be irresponsible to deny the favorable effect and deprive a population historically underserved by our medical system of the resultant improvement in medical management.

Were we justified in conducting A-HeFT only in a population of research subjects self-designated as African-American? The scientific basis of the decision was well-established by previous data in a similarly selected population. One may certainly criticize the criteria used to distinguish the eligible population and one may raise concerns about economic incentives relating to the resultant patent extension, as Professor Bloche has.<sup>9</sup> But the fact is the study was done and that African-Americans with heart disease were offered a longer and healthier life. Should we have studied non-

black subjects as well? We certainly could have, but on the basis of our prior data suggesting a differential response, it would have been inappropriate to study the two populations in a single trial. When a researcher has previous data and mechanistic support for a differential response in two identifiable subpopulations – whether based on demographics, physiologic phenotype or background therapy – it is prudent that randomization be restricted to one subpopulation or be stratified by the critical variable in the two subpopulations. Failing to do that could result in an imbalanced randomization that might have a significant impact on the observed treatment effect. Thus a trial in a white population can and should be done. Whose responsibility it is to perform such a trial is unclear.

Does the success of A-HeFT presage a change in clinical trial design? I think it may. “Evidence-based medicine” has become standard disease-management practice.<sup>10</sup> Yet the evidence cited usually comes from large-scale trials focusing predominantly on white males. A-HeFT raises the possibility that such trial results cannot necessarily be extrapolated to the whole population. In the face of population differences, is it better to carry out a large trial and attempt to examine subgroups for the purpose of identifying efficacy in various subpopulations? Such subgroups, especially defined by race or ethnicity or even gender, are rarely large enough to document efficacy or lack of efficacy. Instead, is it preferable to carry out separate trials in each population subgroup to document the magnitude of efficacy and safety in specific populations, as we did in an African-American population in A-HeFT? I suspect this issue will be the subject of considerable debate in the next few years.

Management of heart failure has reached a critical stage. We need improved precision. Large-scale trials have provided evidence that at least six drugs may be required for optimal outcome. Do all patients need all six drugs, a strategy that is both complex and expensive? Or can we improve precision by carrying out studies focused on specific subgroups that may vary in mechanism of disease and response to individual drugs? We need to better define which patients require which drugs.

Progress requires that everyone accept the fact that subpopulations may and do differ in disease mechanism, prevalence, and therapeutic response. We must agree on the facts and then work together to refine our criteria for distinguishing different populations, whether by genotype, phenotype, or other criteria yet to be identified. The future of medicine depends on improvement in the precision of preventive, diagnostic, and therapeutic efforts that can be used effectively by health care providers in the management of individual patients, appropriately identified by characteristics of medical relevance.

## References

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