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EDITORIAL COMMENT

Understanding and Eliminating Racial Disparities in Transplantation

Still a Ways to Go*

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Heart transplantation (HT) programs are burdened with a heavy responsibility. They are given a precious and limited resource, donated organs, and are charged with distributing them equitably to patients while at the same time maximizing clinical outcomes. Individual HT programs go to great lengths to ensure that all patients enjoy the full promise of HT, namely a return to a normal lifestyle without the risk for premature death. For their part, the Organ Procurement and Transplant Network contractor, the United Network for Organ Sharing, has created an organ-allocation system designed to be fair and balanced, and, even though it requires tinkering from time to time, it is structured to eliminate disparities in access.

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Therefore, it is upsetting to know that, despite these noble efforts, racial and ethnic disparities continue to exist within the field of HT. It has been recognized for years that black and Hispanic patients with heart failure are less likely than are white patients to be referred for transplantation, and that outcomes in nonwhite transplant recipients are inferior to those of white recipients (1–3). Black patients experience higher rates of rejection, allograft failure, and death following transplantation compared with those in white, Hispanic, and Asian recipients. They are less likely to maintain a therapeutic level of immunosuppressant medication and are more likely to require hospitalization. Although there is some good news in that the proportion of transplantations performed in nonwhite patients has increased over the past 2 decades, the gap in survival between white and black recipients has not narrowed (2,4).

Many explanations have been offered to account for these persistent disparities in HT outcomes (2–4). In general, nonwhite patients listed for transplantation have been younger, with a more adverse clinical risk profile, including higher rates of diabetes and renal failure. Black and Hispanic patients tend to come from a more challenging socioeconomic environment, with lower rates of college education and higher rates of Medicaid/Medicare insurance, and from neighborhoods with a lower mean income. Yet, even after adjusting for these factors, the mortality rate in black patients continues to exceed that in white and other nonwhite recipients, suggesting that something other than recipient, transplant, or socioeconomic factors explains these differences.

It has been noted that the higher rates of death from graft failure or other cardiovascular causes experienced in black recipients may be a consequence of less intense immunosuppression (2). Compliance with immunosuppressive medication has been reportedly lower in black HT recipients, but the issue may be more complex than it seems. Self-identified blacks and African Americans are more likely to be expressers of the *CYP3A5*1* genotype, which has been associated with higher clearance and lower bioavailability of tacrolimus (5). Such patients may require 2 to 4 times the dose taken by so-called "slow metabolizers," who are homozygous for the *CYP3A5*3* allele and are more likely to be white, Asian, or Hispanic. The perceived need for much higher dosing to achieve a therapeutic drug level could be mistakenly construed as noncompliance. The consequences of underdosing on the physician's part or missing a dose on the patient's part are likely to be greater in rapid, as opposed to slow, metabolizers.

The role of human leukocyte antigen (HLA) matching in determining transplantation outcomes has been controversial. Due to genetic heterogeneity, nonwhite transplant recipients typically have a greater degree of donor-to-recipient HLA mismatch, and this may contribute to higher rates of allograft rejection without necessarily reducing survival (3). On the other hand, black patients have higher levels of circulating HLA antibodies, which do adversely affect clinical outcomes before and after transplantation. Such sensitized patients with elevated panel reactive antibody (PRA) concentrations wait longer to find a suitable donor, are less likely to receive a transplant, and may have reduced survival after transplantation. Whether there is a significant effect of race and ethnicity on clinically significant sensitization, and whether such differences help to explain the disparity in transplantation outcomes, remain unclear.

In this issue of the *Journal*, Morris et al. (6) sought to address this controversy by exploring the influence of race and alloantibody sensitization on wait-list characteristics and graft survival. They analyzed the Organ Procurement and Transplant Network database for HTs performed between 2000 and 2012 and came to the following conclusions. First, black and Hispanic patients have higher rates of graft failure

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than do other racial groups, and the rate of graft failure is highest in sensitized black patients. Second, HLA mismatch does increase the likelihood of graft failure, and nonwhite recipients are more likely than are white ones to have HLA mismatch. Finally, despite having a higher PRA and greater HLA mismatch, Asian transplant recipients appear less likely to experience rejection or graft failure than white recipients. Additionally, they confirmed previous reports showing that black, Hispanic, and sensitized patients wait longer than others for a transplant. After transplantation, among nonsensitized patients, blacks were the most likely to be treated for rejection, whereas race/ethnicity had no influence on the rate of treated rejection among those with an elevated PRA.

Do immunologic differences fully explain the disparities in graft survival between white and nonwhite transplant recipients? In short, they do not. Although black patients were more often sensitized, this difference was no longer significant after controlling for such things as age, renal function, donor ischemic time, insurance status, level of education, and HLA matching on multivariate analysis. Black race itself remained a predictor of adverse graft survival. On the flipside of the coin, despite higher PRA and greater HLA mismatch, Asian recipients enjoyed a graft survival at least as high as that in whites. Therefore, although sensitization, HLA mismatch, and lower socioeconomic status were more prevalent among nonwhites, these factors alone cannot explain the disparities encountered in black and Hispanic recipients.

We are left with 2 profound questions: What then accounts for the persistent discrepancies between various racial and ethnic recipients?; and, most importantly: What do we do to overcome them? This provocative report by Morris and colleagues illuminates our understanding of the role of race and encourages further research into healthcare disparities, but cannot fully answer the first question. Cultural insensitivity, language barriers, bias, and other unaccounted for socioeconomic factors may still be influencing transplantation outcomes at a level that cannot be captured in currently constructed databases. Even in the present study, 40% of patients were excluded from review due to incomplete data reporting, and no adjustment was made for transplantation-center volume. Black and Hispanic patients are more likely to receive transplants at small-volume centers, which may affect survival outcomes. Prospective observational trials, biomarker research, and an improved understanding of pharmacogenomics should help to elucidate the biological and behavioral differences producing racial disparities.

In the meantime, even in the absence of a clear understanding of the complex origin of care disparities, one can overcome them by being sensitive to the fact that race and ethnicity influence outcomes. By instituting guideline-based, protocolized care, by rigorously implementing performance-improvement measures, and by ensuring access to care, transplant programs should be able to provide quality care to all recipients. Such programs that deliver intensive, comprehensive, multidisciplinary care have produced similar survival rates in white and nonwhite patients, even in the face of unequal rates of allograft rejection (3). This type of care typically encompasses aggressive risk-factor modification, engages patients and families in disease-management programs, and provides sufficient levels of immunosuppression to prevent recurrent rejection and graft loss. This multimodal approach should ensure that all patients enjoy the full promise of HT, regardless of race or ethnicity.

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