Using and Misusing Statistics

What Do We Know About the Effects of Race on the Impact of β-Blockers?

Stephen S. Gottlieb, MD

“The common errors … are not due to an absence of knowledge of specialized statistical methods or of mathematical training, but usually to the tendency of workers to accept figures at their face value without considering closely the various factors influencing them—without asking themselves at every turn ‘what is at the back of these figures? What factors may be responsible for this value? In what possible ways could these differences have arisen?’ That is constantly the crux of the matter.”

—A. Bradford Hill, 1937

Comparison of the response of patient subgroups to proven therapy is fraught with danger. Whether considering the possible benefits of carotid endarterectomy in women, various antihypertensive therapies in very old patients, or β-adrenergic blockade in black patients, the results of randomized studies may be inconclusive.

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There are many reasons for the difficulties we face in applying large studies to our patients. First, studies are powered for the overall population. Thus, we should not expect all subgroups to show benefit. The lack of benefit in a subgroup may merely be the consequences of an underpowered analysis. Second, subgroups may vary in many characteristics, some of which might explain a different finding than seen in the overall study. Lack of compliance, socioeconomic differences, varying severity of disease, comorbidities, and genetic variation could all contribute to a differential subgroup response. Third, the artificial nature of studies might not represent an effect of a drug when real-world follow-up and care are provided. Fourth, the power to see gradations in response is much less than to simply see whether there is any benefit.

All of these issues have been raised with regard to the use of β-adrenergic blockers in black patients. Subgroup analyses have come to different conclusions about their benefit. The negative findings of BEST (Beta-Blocker Evaluation of Survival Trial) were ascribed to the patient population, and genetic differences hypothesized. In contrast, the small black population in MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure) appeared to show benefit. Conflict retrospective and subgroup analyses demand further exploration of this clinically important debate.

In this issue of Circulation: Heart Failure, Lanfear and colleagues do an admirable job in addressing some of the issues that might impair understanding of the effects of race on response to β-blockers. Lack of compliance with medications can be a limiting factor in determining the biological effects of a medication; how can a drug work if the body is not exposed to it? Socioeconomic concerns could certainly have led to lower compliance (and efficacy) in some of the randomized trials. Ascertaining the number of prescriptions filled (and the doses prescribed) may not be perfect, but it is probably the best that can be done to know what medications patients are actually taking.

This study addresses many of the limitations of large randomized studies. It analyzes real-world patients, and the use of all patients from a complete database eliminates selection bias and the impact of increased quantity and quality of care that is inevitable in a randomized trial. Importantly, it accounts for both prescribing patterns and compliance. Whether because of physician fear or the impediments of obtaining medications, many patients take lower doses than those proven to be of benefit, and the effects of such doses need to be understood.

Adjusting for many covariates, a dose response was seen in the end points of mortality and hospitalization. The observed benefit supports the efficacy of β-blockers in patients with heart failure. It implores us to encourage physicians to use the proven doses, and the finding that both whites and blacks showed benefit supports the current advocacy of widespread use of β-blockers. It is therefore heartening to see that β-blocker exposure was a surprisingly high 80% in both blacks and whites. Although it was true that the mean exposure, taking into account the usual underdosing of β-blockers in clinical practice, was a more disconcerting one quarter of the target dosing; again, there was no difference seen by race.

It is necessary, however, to delve deeper to examine other implications of this study. Should we accept the assumption that blacks respond differently based on the results of this analysis? Do the results of this study support the conclusion that β-blockers appear to be 40% to 50% less effective in preventing death or hospitalization among black patients?

Unfortunately, there are a number of factors that should make us wary of the authors’ conclusions. First, the black
patients were very different from the white patients. Not surprisingly, they were younger, with less coronary artery disease and a higher incidence of hypertension. They had better outcomes, consistent with the nature of the patients studied and contrary to expectations of worse care for blacks. When subgroups are very different, statistical analysis cannot be expected to control for all variations.

The proportion of patients with coronary artery disease was greater in whites, and certainly β-blockade may have different effects in such patients. A differential response, therefore, would not say anything about efficacy in patients of different races with the same underlying etiology. Similarly, the presence of hypertension was a covariate, but this did not control for the extent of the hypertension. The use of patients with an ejection fraction of up to 50% further exacerbated such problems, undoubtedly leading to the inclusion of many patients with primary hypertension rather than a cardiomyopathy.

A problem with any retrospective analysis of β-blockers is that sicker patients are less likely to receive high doses. For example, in MERIT-HF, patients randomized to placebo were much less likely to receive or tolerate high doses of inactive study drug if their condition was classified as New York Heart Association functional class III and IV as opposed to class II.5 Because it is impossible to control for all of the factors that might lead a physician to be concerned about a patient, it is inevitable that patients receiving lower doses will have a worse outcome. Thus, in retrospective studies, the consistency of a result, its relationship to a priori hypotheses and prior studies, and its reproducibility must all be considered in interpreting the statistical analyses. In the present study, analysis of the pharmacological effectiveness of the intervention (eg, the effect on heart rate) might have been helpful in determining whether the response of the drug varied between subgroups.

Considering all the limitations of a retrospective population-based analysis, I believe that the results of the study by Lanfear and colleagues must be considered equivocal as to whether there are differential effects of β-adrenergic blockers by race. As is stated in the foreword to Sir A. Bradford Hill’s classic Principles of Medical Statistics, “Often, unfortunately, the figures used are either insufficient in number or documentation or too limited in their scope to bear the weight of the interpretation that is placed on them.”6 Retrospective database studies provide opportunities to discern conclusions that are otherwise impossible to determine. However, we should not be lulled into accepting the results of statistical analyses without considering all their limitations.

**Disclosures**

None.

**References**


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