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## Arguments prove nothing unless verified. A commentary on Kaufman's "Epidemiologic analysis of racial/ethnic disparities: Some fundamental issues and a cautionary example"

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"The strongest arguments prove nothing so long as the conclusions are not verified by experience. Experimental science is the queen of sciences and the goal of all speculation."

Roger Bacon (1214–1294), philosopher and advocate of modern scientific method.

Jay Kaufman has attempted to provide a scholarly assessment of pitfalls in attempting to assign the cause of disease outcomes to apparent racial differences (Kaufman, 2008). Apart from a number of factual errors in his arguments, he has continued to follow the same path as other authors, whom he appears to deride, in misinterpreting the conclusions of our 2001 paper, "Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction" published in the *New England Journal of Medicine* (Exner, Dries, Domanski, Cohn, 2001).

Despite Kaufman's assertions, the matched-cohort design we used in our retrospective analysis of

"Studies of Left Ventricular Dysfunction" (SOLVD) data was not an attempt to replicate a randomized controlled trial but to improve, albeit with remaining inequalities, our ability to identify potential reasons for previously reported differences in outcome (Dries et al., 1999). Our analysis was never suggested to be more than hypothesis generating. The over-interpretation by Kaufman and others served their purposes, not ours. In addition, his criticisms of our analytic approach are mostly inaccurate.

Our statements in the *New England Journal of Medicine* article were intentionally worded to discourage mis-interpretation or over-interpretation of our findings. Since prior heart failure trials were conducted predominantly in white subjects and possible differences of response in blacks were uncovered it was correct to state that "the overall population of black patients with heart failure may be underserved by current therapeutic recommendations" and "it seems appropriate to consider current therapeutic recommendations as applying to white patients but not necessarily to black patients". These comments are clearly in the context of a hypothesis, not a definitive conclusion. Our recommendation for "clinical trials in black patients that are designed prospectively to evaluate therapeutic responses..." (Exner

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et al., 2001, p. 1357) further emphasized our recognition for the need of additional, prospective randomized data.

We recognize that our matched-cohort design, as with any study of this kind, was imperfect. Yet, many of Kaufman's criticisms are unmerited. Our matching strategy was described as "questionable because race was not randomized" (Kaufman, 2008). The matching method used was both appropriate and scientifically valid. The comment that "once the data are already collected, however, one can't generally do better by throwing away a large proportion of these data" (Kaufman, 2008) is erroneous. In fact, a paper used to support Kaufman's criticisms states that "matching can be expected to increase efficiency" when both the matching variables, and exposure, self-identified race, are negatively associated with outcome (Greenland & Morgenstern, 1990). That was the situation for our analysis. Despite Kaufman's assertions related to our statistical models, we were cognizant of issues related to residual confounding and misclassification and used great care to deal with these issues as best we could. We acknowledged these limitations in our paper by stating that "no degree of statistical adjustment can ensure complete comparability" (Exner et al., 2001, p. 1357). Further, the comment that "it is well appreciated in the theoretical epidemiologic literature that groups with higher baseline risk will in general have more modest response to treatment... (Maldonado & Greenland, 2002)" (Kaufman, 2008, emphasis added) is inaccurate. This theoretical concept is not universally accepted (Dawid, 2002). Moreover, it is well known that patients with left ventricular systolic dysfunction and a higher baseline risk derive greater benefit from therapeutic interventions, in terms of absolute benefit, than do patients with a lower baseline risk (Moss, 2000; Sheldon et al., 2000).

It is clear that a therapeutic reduction of hospitalization rate is a particularly sensitive guide to efficacy in sicker patients, as evidenced by its usefulness in recent studies in advanced Classes III and IV heart failure (Packer et al., 2001, 2002). Indeed, Kaufman uses mortality as a guide to severity of heart failure, even though differences in mortality, comparing white and black patients, may be a result of health management disparities. Furthermore, Kaufman claims that in our paper "the null finding for mortality is largely ignored..." (Kaufman, 2008). In doing so he fails to appreciate that in the SOLVD Prevention Trial, which was the source of most of our black patients, mortality was not reduced by enalapril in the overall population (SOLVD Investigators, 1992). We also clearly reported that differences in rates of hospitalization for heart failure were

responsible for the differences in outcome that were observed between the two groups. The abstract to our paper specified "no significant change in the risk of death was observed in association with enalapril therapy in either group" (Exner et al., 2001, p. 1351). These data were further highlighted in Table 3 of our paper and specific comments were made that "mortality was similar among the black patients and the matched white patients regardless of treatment assignment" and that "no significant alteration in mortality was observed in association with enalapril therapy" (Exner et al., 2001). Thus, it is neither surprising nor unexpected that subsequent analyses (Dries, Strong, Cooper, & Drazner, 2002; Shekelle et al., 2003) have confirmed our findings.

The analysis we reported in 2001 never attempted to identify genetic or environmental factors that might contribute to our observations. Studies demonstrating lesser antihypertensive potency of ACE inhibitors in black than in white hypertensive patients (Cohn et al., 2004) also have made no such attempt. On two points we agree with Kaufman. The findings from our paper have been both over-interpreted and mis-interpreted by others. Our analysis was conducted to investigate whether observed differences in outcome could, in part, be explained by differences in therapeutic response. If confirmed, we planned to conduct additional, definitive research in this area aimed at improving the lives of patients with heart failure. This research has been completed. We also agree that a "randomized controlled trial (RCT) is widely considered to be the gold standard for establishment of causality in biomedicine" (Kaufman, 2008). Our analysis has been followed by at least one prospective randomized trial designed to address therapeutic response in a self-identified black population with heart failure (Taylor et al., 2004), and that trial has identified a therapy that reduces mortality, reduces hospitalization, and enhances quality of life in these patients. Such data are critical both in providing valid evidence and in assisting physicians in treating individual patients.

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