Like the famous dog in the night in Conan-Doyle’s Sherlock Holmes mystery, Silver Blaze, the study by Khazanie et al1 in this issue of Circulation: Heart Failure is most remarkable for what it does not do, rather than what it does do. It represents a well-intentioned attempt to fill a large knowledge gap on the impact of treatment with combined nitrates and hydralazine (ISDN/HYD) on outcomes in patients with heart failure and reduced ejection fractions (HFrEF). This detailed analysis of a heterogeneous observational cohort seems to examine the broader application of the findings from the sole contemporary randomized controlled clinical trial of ISDN/HYD, the African American Heart Failure Trial (A-HeFT).2 Completed 11 years ago, the A-HeFT trial found a 47% reduction in mortality associated with treatment of ISDN/HYD added to neurohormonal blockade.2 Despite this hefty mortality benefit, and a recommendation by the American Heart Association/American College of Cardiology Guidelines for the Management of Heart Failure1 for usage in self-identified blacks with class III–IV HFrEF (class I indication, level of evidence, A), usage of the combination has remained remarkably low and still more remarkably no further clinical trials that would generate data that could be classified as level of evidence A have followed. There are 2 questions prompted by this study: first, does the current analysis help us to better understand the treatment of HF with this drug combination, and second, what do we really need to better understand the use of ISDN/HYD in HFrEF?

See Article by Khazanie et al

Khazanie et al1 used an observational study design and registry data of patients with HFrEF generated from the American Heart Association’s Get With the Guidelines-HF project linked to Medicare data, to relate all-cause mortality, all-cause readmission to hospital, and cardiovascular readmission to hospital with treatment with ISDN/HYD. The cohort is divided into 4 groups: treated and untreated blacks and treated and untreated other race (OR) subjects. Of note, there are significant differences within the cohort in baseline characteristics in this analysis, and the cohort differs significantly as well from the cohort studied in A-HeFT. This cohort is significantly older by 18 to 23 years (mean age of blacks in this study was 75 years and ≈80 years in ORs when compared with a mean age of 57 years for both treatment arms in A-HeFT).2 Surprisingly, the investigators included only subjects of ORs who had a specific contraindication to angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blockers (ARBs) treatment, rationalized by the likelihood that treatment with ACE-I/ARBs would be indicative of more severe hypertension. Because 90% of the A-HeFT cohort and 60% to 80% of people aged >65 years have hypertension, it is not intuitive that hypertensive OR subjects should have been excluded. The full range of reasons for contraindication to ACE-I or ARB in the OR group and non-treatment in the black group could not be fully gleaned from this registry because treatment was at the discretion of the patient’s physician. The end result, however, is that the black and OR subjects within the cohort received treatments different from one another and different from treatment received by subjects in the A-HeFT cohort (93% received either an ACE-I or ARB). Even in those A-HeFT subjects >65 years of age, ≈90% received either ACE-I or ARB.3 Lower rates of treatment with other guideline recommended therapy were observed in both racial groups of the current cohort, a finding commonly reported in elderly subjects with HF. However, this is also in marked contrast with the A-HeFT cohort, which was well treated with other neurohormonal blockade. These baseline treatment differences and extreme potential for selection bias in those who received ISDN/HYD make the interpretation of outcomes by treatment group and race, and the comparison with the results in A-HeFT challenging. In addition, dementia was reported to be present in >300 registry subjects, not surprising in an elderly cohort, but a condition that would lead to exclusion from most clinical trials because of its impact on disease treatment goals, management, and medication adherence.

The key finding of the analysis was that there were no differences in outcomes between treated and untreated subjects of either racial group, contrary to the findings in A-HeFT and the earlier V-HeFT trial.1,2 It is particularly relevant to note that these findings are sharply at variance with the post hoc analysis of the elderly subjects in A-HeFT where treatment with ISDN/HYD resulted in significant reduction in the combined end point of mortality or first HF hospitalization.4 Because these findings are different from outcomes previously reported in 2 randomized clinical trials,2,5 how should these data be interpreted? Unfortunately, although the discussion diligently lists potential factors that might explain the difference in these findings when compared with those of the A-HeFT, no new
hypotheses or insights are offered. Finally, but most importantly, the authors mention the significant limitations imposed by the observational nature of this study. These limitations are, in fact, substantial and raise the question of the relevance of the conclusions on outcomes of this treatment from this analysis. It is highly likely that these data would not be considered evidence sufficient to support recommendations for or against usage of ISDN/HYD in clinical care guidelines.

This analysis also importantly calls into question the principles of what constitutes valid evidence supporting the efficacy of therapeutic interventions. We have long since learned about the dangers of the use of observational data as evidence of therapeutic efficacy from examples, such as the differences between observed effects of hormone-replacement therapy or antioxidant supplementation, when compared with measured outcomes of carefully done clinical trials.

Thus, the question is what would justify using this kind of analysis to define the efficacy of a treatment protocol when data from randomized controlled clinical trials that demonstrated significant benefit of the treatment are available? Does this analysis actually help to fill the knowledge gap that has so stubbornly persisted surrounding this therapy? This first question leads quickly to the paramount question so carefully avoided in this analysis, as well as its discussion. That critically important question is why (11 years after the completion of a positive randomized double-blinded, controlled clinical trial in a well-matched, well-treated cohort that demonstrated a 43% reduction in mortality) there have been no new clinical studies to either confirm or deny these findings? Why there have been no studies designed to understand mechanisms or to extend the findings of the A-HeFT trial to other HF populations, despite the increasing incidence of HF in the United States? The answer may lie in the social discourse firestorm surrounding race in medicine that was ignited by A-HeFT and was unlike any other discussion about a positive clinical trial. Popular press headlines at the time suggested that America was now moving toward race-based medicine, the ethics of ever considering race in medicine were questioned, and it was feared that a medicine tested in an all black cohort would pose a danger of stereotyping in the doctor’s office. The truth of the matter is that heart failure clinical trials, with rare exceptions, have always been predominantly racially homogeneous, starting with the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial in 1986, a study of 253 racially homogeneous patients (in this instance, all Scandinavian) with advanced heart failure. However, a positive clinical trial in a narrow population should ideally be followed by studies that delineate, with high-quality evidence, other populations with significant disease burden that might benefit from treatment. Unfortunately, clinical trial subjects subsequent to a bellwether trial have, more often than not, remained relatively homogeneous with respect to race/ethnicity and sex. Thus, the quality of evidence for treatment efficacy in so many instances in demographic groups other than majority men is substantially weaker. An excellent example of this is the use of ACE-I in women with HFrEF. Despite the fact that women make up >50% of the population with HF, their inclusion in clinical trials has been much lower, so that the data on women treated with ACE-I are entirely based on meta-analyses and post hoc analyses. These data suggest a lesser effect in women, but this suggestion is derived from lesser quality data. This same assertion could be made on the data for the efficacy of these agents in blacks. Ironically, A-HeFT was harshly criticized for doing a study in a group of patients historically consistently denied inclusion in other HF clinical trials, but in the time since completion of the trial, no effort has been made to understand whether other populations might benefit.

The omission of minority racial/ethnic groups from clinical research that determines optimal treatment strategies has been and remains a powerfully damaging intersection of race and medicine. Studies of most therapeutic agents in cohorts predominately of European descent have made little or no attempt to determine whether the effects of these agents were truly applicable to other racial groups.

At this juncture in time, it is critical that we think deeply about the history of inclusion in and benefit from clinical trials in the United States as we, as a society, embark on the next major and most promising initiative in American medicine, precision or personalized medicine. For precision medicine to be personalized and precise for everyone, we will need to honestly grapple with and come to terms with race as a factor in health and disease. This will require that the biomedical research enterprise recognize and remediate the omission of specific racial groups from every aspect of healthcare research. Consideration of the health impact of race from sociopolitical to genetic factors must be done with fairness and with the committed goal of optimal health for everyone.

So, like the dog in the Sherlock Holmes mystery, this study does not truly alert us to new information that would fill the large knowledge gap on treatment of HFrEF with ISDN/HYD. It does remind us, however, that thoughtful, honest consideration of race in the context of precision medicine is needed to make medicine truly personalized and precise for everyone.

Disclosures

None.

References


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