Dilemmas With Race and Heart Failure Treatment

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The combination of hydralazine and isosorbide dinitrate (H+ISDN) provides balanced vasodilatation, resulting in afterload and preload reductions in heart failure (HF). Both the V-HeFT (Vasodilator Heart Failure Trials) I and II showed improvement in functional capacity and ejection fraction with the use of this combination in HF patients with reduced ejection fraction.[1] Subsequent secondary analysis of the V-HeFT data suggested that there might be a race-dependent response to H+ISDN therapy, with blacks deriving more benefit.[1] In parallel, there was progress in understanding the role of oxidative stress in HF, varying racial trends in oxidative stress, and the role of H+ISDN in this respect, with ISDN donating nitric oxide and hydralazine being an antioxidant. The hypothesis drawn from these observations was tested in A-HeFT (African-American Heart Failure Trial), which was terminated early because of a 43% relative risk reduction in mortality with H+ISDN observed during data monitoring and led to the approval of BiDil (fixed-dose H+ISDN formulation used in A-HeFT) for the treatment of HF in self-identified blacks.[2] This approval was the first where race was used to identify the target population.

Although A-HeFT showed the efficacy of H+ISDN in blacks, it did not show H+ISDN to be nonefficacious in non-blacks. Although non-blacks patients did not seem to derive mortality benefit in a retrospective analysis of V-HeFT I, this subgroup finding should be viewed with caution. Rather than reviewing an individual subgroup, the statistical standard is to assess treatment-by-subgroup interaction, which was not provided in this analysis. These data are limited by wide confidence intervals, and the study was not powered to assess either noninferiority or superiority versus placebo in blacks or non-blacks. There were improvements in ejection fraction and exercise tolerance in non-blacks treated with H+ISDN; both surrogates that have been associated with survival in HF. There was no difference in all-cause or HF hospitalizations between blacks and non-blacks. Thus, these mortality data may represent chance finding, and the role of H+ISDN in non-black patients remains uncertain.

The clinical value of H+ISDN in non-black patients has not been confirmed, despite 3 decades of encouraging data. There are several obstacles to such investigation. H+ISDN are both generic and available inexpensively. Although some have advocated adhering to the proprietary fixed-dose combination because uncertainty that different pharmacokinetic characteristics of the generic agents may result in nonreplication of A-HeFT results, the majority of prescriptions for the combination have been for generics. There is no commercial case for a private concern to support such a trial using generic preparations. Conversely, the use of proprietary fixed-dose formulation has remained low in practice. Public funds do not generally support excluding race- or sex-based subgroups from research unless biologically justified. Hence, a trial excluding blacks is deemed not optimal. On the basis of A-HeFT results, randomizing blacks to placebo is also considered unethical. However, the independent clinical contribution of the 2 components of the combination has never been evaluated. It seems ethical and advantageous to randomize blacks to H+ISDN versus ISDN alone, particularly in the presence of angiotensin converting enzyme (ACE) inhibitors. Intolerance to the combination is a key reason for its underutilization. Nitrates alone are better tolerated and are likely the key therapeutic component of the combination. ACE inhibitors have both the antioxidant and afterload reduction properties afforded by hydralazine and could be used as background therapy.

An analysis of over 54 000 patients with HF from the Get With The Guidelines Heart Failure program revealed that <25% eligible black patients are on the combination, using any formulation, despite guideline endorsement.[3] A subsequent analysis from the same database limited to Medicare population with postdischarge follow-up also showed lower adherence with H+ISDN post discharge.[4] Some argue that randomizing blacks to H+ISDN versus placebo will double their chances of receiving this combination. Others consider this rationale invalid because if eligible black patients are identified, then the ethical mandate is to prescribe H+ISDN rather than to randomize. The problem becomes more complex when considering including blacks in placebo-controlled trials with other agents, for example, phosphodiesterase inhibitors and soluble guanylcyclase stimulators, which are contraindicated in patients taking long-acting nitrates.[5] If it is unethical to include blacks in trials comparing H+ISDN to placebo, then it is equally unethical to enroll them in any trial that precludes H+ISDN use as background therapy. This concern has been ignored in past and ongoing trials, which have included

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blacks in a placebo arm instead of initiating H+ISDN therapy, without having demonstrated intolerance to the combination. Whatever is the correct ethical judgment it should be applied consistently across all trials.

Even if one were to eliminate blacks in any trial where long-acting nitrate use is an exclusion criterion (barring those with known intolerance), is this approach the right one? We argue that it is not. First, race is a suboptimal biological surrogate with no known pathophysiology that is exclusive to a race, even if it is more or less pronounced in any particular race or ethnicity-based subgroup. Hence, it is preferable to segment patients based on pathophysiology and not race. These novel therapies hold promise, as does the possibility for equal efficacy with greater effectiveness (tolerability and adherence) with ISDN+ACE inhibitor, compared with H+ISDN. Not testing these treatment options in blacks is equally problematic as not testing H+ISDN in non-black patients.

All of these issues rest on data that some find unconvincing. A-HeFT enrolled 1050 patients. There was no difference in mortality between the 2 groups for a year after randomization, followed by an uncharacteristic wide separation of survival curves. There were only 86 deaths in the trial (32 in H+ISDN and 54 in placebo arm).[2] Nevertheless, the Food and Drug Administration and guideline panels accepted earlier retrospective analyses of V-HeFT in addition to A-HeFT data, to be adequate for approval and recommendation.

On the basis of the above concerns, there are several choices. If one believes that there remains equipoise around H+ISDN benefit in black patients, then there should be a trial assessing the benefit of H+ISDN versus placebo powered to assess outcomes in both black and non-black patients, to prove benefit in non-black, and to confirm the benefit in black patients. We argue that such a trial should include a nitrate-alone arm, with background ACE inhibitor use. Alternatively if one is confident of H+ISDN efficacy in blacks, then such a trial should be performed in non-blacks. We would argue that such a design would omit examining a critically important question, that is, in blacks, would nitrates+ACE inhibitors achieve a noninferior degree of efficacy, with greater effectiveness than H+ISDN, given improved tolerance and adherence. These questions could all be addressed in a single trial with a novel design that excludes blacks from the placebo arm, testing H+ISDN versus placebo only in non-blacks, whereas testing efficacy noninferiority and superior tolerance between the H+ISDN versus ISDN+ACE inhibitors in all patients. Alternatively, there could be 2 trials: a 3-arm trial in non-blacks and a 2-arm (no placebo) trial in blacks. We view the latter as less desirable because we should be moving to test for consistency between black and non-black patients, rather than perpetuating separate investigation. It is essential that we move to answer these critically important questions with major public health implications across all patient populations.

Disclosures

None.

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