JACC: HEART FAILURE
VOL. ■, NO. ■, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2017.05.005

EDITORIAL COMMENT

The Paradox in Demonstrating Hydralazine-Nitrate Efficacy*

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Establishing the clinical effectiveness of hydralazine and isosorbide dinitrate for the treatment of heart failure has taken an unconventional path. Rather than the usual sequence of clinical observations leading to a definitive placebo-controlled trial, the remarkably positive trials have led instead to a search for clinical experience to document effectiveness. This paradox relates to the apparent unwillingness of the medical profession to embrace the definitive results, perhaps because of a number of unusual features of the development process. These are summarized in the following text.

1. The original hemodynamic observations that documented the favorable circulatory effects of the drug combination (1) were not adequate to persuade practitioners that the 2 drugs, readily available, should routinely be prescribed for heart failure.
2. V-HeFT (Vasodilator-Heart Failure Trial), the original clinical trial of the combination, tested a concept, not a pill. The results forced rejection of the hypothesis that any vasodilator that improved hemodynamics would improve survival. It identified a unique benefit of the combination of the 2 generic medications, isosorbide dinitrate and hydralazine (H-ISDN), compared with their placebos in slowing progression of the left ventricular structural abnormality and in dramatically reducing mortality (2). However, the study was small, with only 186 men assigned to the drug combination. Because the generic drugs used in this Veterans Affairs–funded study had been manufactured specifically for the study, and no commercial entity was financially motivated to seek approval from the U.S. Food and Drug Administration (FDA) to market the inexpensive combination therapy, these doses of the drugs were not available for clinical use, and the process of writing prescriptions for both generic drugs in the appropriate dosage was cumbersome.
3. The idea that the drug combination was particularly effective in African-American subjects was based both on known mechanisms and on post hoc analysis of the V-HeFT data (3). By focusing on this unique population, it was possible for a small drug company (NitroMed, Lexington, Massachusetts) to fund a modest-sized trial (A-HeFT [African-American Heart Failure Trial]) with a unique combination pill (BiDil) that facilitated a more conventional placebo-controlled study to document the remarkable benefit of the fixed-dose drug combination (4). FDA approval for black subjects, based on the trial design that the FDA sanctioned, led to a backlash accusation of racism from the very community the study was designed to help (5).
4. Based on the dramatic mortality reduction in A-HeFT (43%) and the expense of the clinical trial, NitroMed marketed BiDil at a price considerably higher than that of the available individual generic drugs (5). Negative publicity hindered their meager sales effort, and the company was sold. The fixed-dose drug has had a re-birth with its new sponsor, but it is still vastly underprescribed.

Ziaeian et al. (6) justify their new analysis in this issue of *JACC: Heart Failure* as an attempt to document "real-world clinical effectiveness" of the drug combination, thus suggesting that controlled prospective trials are not conducted in the "real world."

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

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It is true, of course, that the clinical trial environment excludes many individuals who do not meet the entry criteria and provides oversight of drug utilization not available in clinical practice. However, these efforts are aimed at providing an environment in which testing of the management strategy can be effectively accomplished.

A-HeFT (4) was conducted in a diverse clinical practice setting, including Veterans Affairs hospitals, and thus could certainly be classified as "real world." It used evidence-based background therapy with a fixed-dose combination of H-ISDN or placebo and careful scrutiny of the dosage consumed. In the real world of the Veterans Health Administration electronic medical records, no such features were in place. Only 15% of the apparently eligible population received prescriptions for H-ISDN, and most of the prescriptions were for the individual generic drugs, not the fixed-dose combination that was so effective in A-HeFT. Indeed, pharmacokinetic studies have shown greater bioactivity of the fixed-dose combination as well as some of the formulations used in the V-HeFT trials compared with that of the generic drugs (7). No data are available on what doses of the individual drugs were prescribed, and almost one-half of these so-called "treated" patients did not have the drugs in their possession. This experience emphasizes why observational studies cannot replace prospective trials in assessing the effectiveness of pharmacological agents. A prescription for a drug is not evidence of taking it in an adequate dose. Furthermore, no documentation is provided that the patients who were treated before their hospitalization continued the therapy during the follow-up interval that serves as the basis for the conclusion that the H-ISDN therapy was modestly effective in reducing mortality.

Thus, this Veterans Affairs records analysis serves more as an indictment of clinical practice in the "real world" rather than as a demonstration of the effectiveness of H-ISDN. It is another example of the difficulty in changing practice in response to new clinical trials. The tragedy of the BiDil story is the shortened life expectancy of so many black patients, regardless of how they were identified, who would have survived if they had received BiDil. Furthermore, the magnitude of the likely benefit in a white population has not been assessed. Who would choose to fund such a study? Neprilysin inhibition (8) probably produces effects similar to those of BiDil, but no pharmaceutical company would choose to fund comparative trials.

We are likely to continue reading papers citing the persistently high mortality rate in patients with heart failure as a stimulus for new clinical trials. More widespread use of currently approved and effective therapy could go a long way toward closing the gap between clinical trials and the "real world."

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KEY WORDS heart failure, heart failure with reduced ejection fraction, hydralazine, mortality, nitrates, race