JACC: HEART FAILURE
VOL. 4, NO. 5, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.02.016

Neprilysin Inhibition in the Time of Precision Medicine*

Arthur M. Feldman, MD, PhD

The recent results of the PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) showing that the combination of the neprilysin (NEP) inhibitor sacubitril (sac) and the angiotensin receptor antagonist (ARB) valsartan (sacubitril/valsartan [sac/val]; Entresto, Novartis) decreased the risk of death from cardiovascular cause or first hospitalization for heart failure (HF) while modestly reducing the risk of death from 19.8% to 17.0% (hazard ratio: 0.84) when compared with the angiotensin-converting enzyme inhibitor (ACEi) enalapril engendered considerable interest among cardiologist and HF specialists (1). In this issue of *JACC: Heart Failure*, Dr. Milton Packer posits that since "the PARADIGM-HF trial has demonstrated the need to inhibit NEP, we should do so as early as possible and not delay until we have achieved target doses of a conventional inhibitor of the renin-angiotensin system" (2). He uses the allegory of the novel *Love in the Time of Cholera* to make the point that physicians are having difficulty breaking from their long-standing comfort in using an ACEi as a pivotal therapy for patients with HF and reduced ejection fraction (HFrEF). Written by the Nobel laureate Gabriel García Márquez, *Love in the Time of Cholera* describes how Florentino Ariza meets and falls in love with Fermina Daza, only to have his advances spurned until fate brings them together over 50 years later, albeit with a less than happy ending. This is an interesting allegory to use because Márquez is universally recognized as one of the most preeminent members of a literary movement known as "magic realism" ("marvelous realism") and *Love in the Time of Cholera* is a quintessential example of that genre (3). Magic realism mixes elements of fantasy into otherwise realistic or common settings. As physicians, we must however look at the results of PARADIGM-HF from a realistic and scientific perspective based on the elements that we have used to judge all HF therapies: 1) the pre-clinical data; 2) the design and results of all relevant clinical trials; and 3) associated risks - both observed and theoretical.

PRE-CLINICAL CARDIAC DATA

NEP is a plasma membrane glycoprotein that is a member of the metalloendopeptidase family. Widely expressed in mammalian tissues, NEP is the principle mechanism for degradation of the natriuretic peptides. However, NEP is not precise in its actions—hydrolyzing numerous other peptides including angiotensin I, angiotensin II, endothelin-1, kinins, adrenomedullin, opiod peptides, enkephalin, gastrin, and amyloid beta (Aβ).

Most of what we know about the role of NEP inhibition in the heart and vasculature comes from classical pharmacologic studies begun 2 decades ago showing that NEP inhibition alone resulted in an increase in natriuretic peptides but also in peripheral vasoconstriction (4). When compared with placebo, the combination of a NEP inhibitor (NEPi) with an ACEi (omapatrilat) (5,6) or the combination of a NEPi with an ARB (valsartan) decreased maladaptive cardiac remodeling (7). Omapatrilat was more effective at preventing changes in left ventricular geometry and premature mortality in Syrian hamster cardiomyopathy then was captopril (8). By contrast, in rats with chronic HF, omapatrilat did not result in benefit as compared with captopril (9,10). Similarly, sac/val had no effect on left ventricular remodeling or hemodynamic indices including cardiac output, stroke work, or dP/dt when compared with val in the same model: there was however a significant increase in ejection fraction (11). Thus, the pre-clinical data does not consistently demonstrate robust beneficial effects of NEP inhibition when combined

*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.

From the Department of Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania. Dr. Feldman has reported that he has no relationships relevant to the contents of this paper to disclose.

with an ACEi or an ARB in comparison with an ACE or ARB alone.

CLINICAL EFFECTS OF NEP INHIBITION IN HF

Studies begun 2 decades ago also demonstrated that NEP inhibition alone did not have salutary effects in patients with HF (12). In addition, a phase II study comparing omapatrilat with lisinopril failed to show a difference in the primary endpoint of exercise performance (13). Omapatrilat also failed to meet its primary endpoint of death or hospitalization in the 5,770-patient phase III OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial and was associated with a 2-fold increase in angioedema—leading the sponsor to discontinue its development. Investigators posited that ARBs might be less likely than ACEis to interfere with bradykinin metabolism; thus, the combination of a NEPi and an ARB became a more attractive choice for further development.

The PARADIGM-HF trial was the first large phase III study of a NEPi/ARB to meet its primary endpoint; however, the design of the trial raises important questions. First, the PARADIGM-HF trial compared an optimal (titrated) dose of val/sac with a fixed dose of enalapril (10 mg twice a day): a dose of enalapril that is below the maximum dose recommended by the American College of Cardiology/American Heart Association Practice Guidelines (10 to 20 mg twice a day) (14). That this dose of enalapril may have been inadequate in the PARADIGM trial is demonstrated by the finding that blood pressure was significantly lower after treatment with sac/val than after treatment with enalapril (1).

Blood pressure is an important metric because "high-dose ACE" inhibitors proved more effective than "low-dose ACE" inhibitors when the high-dose ACEi lowered blood pressure more than did the low-dose ACEi but not when the 2 doses had the same blood pressure response. For example, the ATLAS (Assessment of Treatment with Lisinopril and Survival) trial showed only an 8% nonsignificant decrease in mortality with high dose ACEi compared with low-dose ACEi; however, there was a 12% lower risk of death or hospitalization for any reason ($p = 0.002$), 24% fewer hospitalizations for HF ($p = 0.002$) and systolic blood pressure decreased by 4.4 mm Hg more in the high-dose group ($p < 0.001$) (15). Konstam et al. (16) found similar outcomes in the HEAAL (Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure) trial: high-dose lisinopril as compared with low-dose lisinopril met the primary endpoint of death or admission for worsening HF ($p < -0.027$) and there was a 13% reduction in HF admissions ($p < 0.025$) and an 11% reduction in cardiovascular admissions ($p < 0.023$) (16). Furthermore, we demonstrated that in patients with HF, only a high dose of an ACEi diminished the negative impact of the presence of an ACE deletion allele (ACE-D or ACE-DD) that is associated with increased ACE activity and an increased risk of HF-related events (17). Studies that failed to show a decrease in blood pressure with a high dose of an ACEi or an ARB as compared with a low dose did not show any difference in outcomes between the 2 groups (18,19).

There were other factors in the design of the trial that make translation to patient care challenging. For example, a run-in with enalapril preceded the run-in with sac/val. The intent of the run-in period was to ensure that the maximum benefit from sac/val could be achieved by selecting for patients who would most likely tolerate the target doses of both medications; however, this design precludes physicians from understanding the true tolerance to sac/val. In particular, this selection bias may have resulted in an under-representation of angioedema. With only 2 doses evaluated in the trial physicians will face a second therapeutic conundrum: if patients do not reach their target dose of sac/val or if they require down-titration of sac/val because of hypotension, would a prudent approach be to switch patients to their prior dose of an ACEi or an ARB? In fact, 18% of sac/val patients developed symptomatic hypotension. Similarly, because pre-specified subgroup analysis suggested that sac/val was no better than enalapril in treating patients with New York Heart Association functional class III/IV symptoms, should patients who progress to worsening symptoms while on therapy be switched to an ACEi, an agent known to benefit patients with severe disease (20). Despite an overwhelming percentage of patients having an ejection fraction ≤35%, only 15% of patients enrolled in the trial had received an implantable cardioverter-defibrillator (a Class 1A recommendation) and only 7% of patients had received cardiac resynchronization therapy—raising the possibility that mortality rates might have been lower and the effect of drug therapy less evident had more patients been receiving what is considered appropriate therapy in the United States (14). Sac/val significantly increased the ratio of urine albumin to creatinine when compared with enalapril, a difference that could reflect worsening renovascular disease. Finally, it should be noted that treatment with sac/val can also impair monitoring of chronic HF patients with B-type natriuretic testing (21).