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Please note: Drs. Pareek, Mehta, Purkait, and Grover are employees of Ipca Laboratories, Ltd.; and are involved in research studies of chlorthalidone.

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REPLY: Diabetic Hypertensives and Diastolic Dysfunction: Use of Calcium-Channel Blockers—A Clinical Concern

Dr. Pareek and colleagues make several interesting points regarding our paper (1). We agree that SGLT-2 inhibitors have not yet been specifically evaluated for safety and efficacy in HF, including in patients with diabetes. However, the SGLT-2 inhibitor empagliflozin has recently demonstrated an unprecedented 38% reduction in cardiovascular mortality, which might be due at least in part to a reduction in heart failure (HF) (2). These results have gathered strong interest in the scientific community to test the hypothesis of whether SGLT-2 inhibitors should be considered standard HF treatment, even in HF patients without diabetes, and randomized controlled trials are currently underway testing this hypothesis.

The exact sequence of adding antihypertensive agents in HF with hypertension certainly is debatable (we suggested calcium-channel blockers [CCBs], followed by spironolactone and then a thiazide-like diuretic in patients with HF with preserved ejection fraction [HFpEF]). We selected CCBs in HFpEF as initial antihypertensive therapy because CCBs improve left ventricle (LV) filling, and the use of amlodipine was documented to be safe in HF (3,4). As opposed to amlodipine, there are no safety data for thiazides or thiazide-like diuretics (chlorthalidone or indapamide) in HF. There is no question, however, that in hypertension, thiazide-like diuretics are outstanding agents for preventing HF.

Of note, the whole question as to the sequence of adding drugs is somewhat academic. We merely are providing our opinion on how to treat residual hypertension in HF (and not how to treat HF per se); there is no iron-clad evidence or head-to-head comparison of safety and efficacy among various antihypertensive drug classes in HF.

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An Opportunity to Definitively Evaluate the Theoretical Risks of Neprilysin Inhibition

Solomon et al. (1) recently described the rationale and design of a trial aimed at identifying the potential utility of the combination of the angiotensin receptor antagonist valsartan and the neprilysin inhibitor sacubitril (Entresto) for the treatment of individuals

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with heart failure and preserved ejection fraction (HFrEF) (1). Identifying therapeutic efficacy in patients with HFrEF is challenging, and the investigators have given great thought to the design of the trial. Although the investigators have also tried to address the important question of whether sacubitril exacerbates Alzheimer's disease (AD) (2), their approach falls short of current guidelines. They propose to carry out a substudy that will measure cognitive function in study patients by using the Mini-Mental State Examination (MMSE) instrument. Although the MMSE is a useful screening instrument that clinicians can use to assess progression and severity of cognitive impairment, it is not diagnostic for Alzheimer's disease. The International Working Group and U.S. National Institute on Aging-Alzheimer's Association have developed guidelines for the diagnosis, staging, and clinical investigation of AD that call for both appropriate cognitive testing (e.g., episodic memory tests with established specificity for AD) and in vivo evidence of AD pathology (e.g., increased tracer retention in amyloid positron emission tomography [PET] or decreased $A\beta_{1-40}$, together with increased T-tau or P-tau in the cerebral spinal fluid) (3). Using the right tests is of more than academic importance because heart failure patients have multiple risk factors for the development of cognitive dysfunction that can wax and wane and are independent of AD (4). Thus, simply measuring cognitive function can give ambiguous information that could bias the results in either direction. In fact, the U.S. Food and Drug Administration's (FDA) approval letter for the New Drug Application for sacubitril stated: "based on appropriate scientific data, FDA has determined that you [the sponsor] are required to conduct the following: A multicenter, randomized, double-blind, active-controlled trial to evaluate the effects of Entresto compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and PET imaging in patients with chronic heart failure with preserved ejection fraction" (5). The FDA is calling for the right studies; the investigators should follow their mandate so that we can all use this important new drug with a clear conscience.

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Please note: Dr. Feldman is the founder of and holds equity in Renovacor, Inc.

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REPLY: An Opportunity to Definitively Evaluate the Theoretical Risks of Neprilysin Inhibition

As neprilysin is 1 of several proteases that plays a role in the degradation of amyloid β proteins, concern has been raised about the theoretical possibility that long-term neprilysin inhibition could influence the development of Alzheimer's disease (AD); yet the specific role of neprilysin in the pathogenesis of AD remains unclear. In addition to the likely redundancy in the enzymes that break down amyloid β, individuals with truncating mutations in the gene encoding for neprilysin, who have total neprilysin deficiency, appear to lack any phenotypic consequence (1). Moreover, in individuals with amyloid precursor protein or presenilin mutations, lifelong increase in cellular production of pathogenic amyloid β_{1-42} by 40% to 50% or more do not result in clinically noticeable cognitive symptoms until the fifth or six decades. Human experiments with sacubitril/valsartan in volunteers did not show selective elevation of the toxic form of amyloid β_{1-42} (2); and in the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial (N = 8,399 participants with follow-up of up to 4.25 years) there were no observed increases in adverse events secondary to dementia (3), although comprehensive cognitive function testing was not performed.

Nevertheless, these theoretical concerns have prompted several specific proactive approaches on the part of the manufacturer of sacubitril/valsartan and sponsor of the PARAGON-HF (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with