The PARADIGM-HF trial

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TO THE EDITOR: Two considerations concerning the interpretation of the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial are not addressed in the article by Sabe et al regarding a new class of drugs for systolic heart failure.[1] First of all, the PARADIGM-HF trial compared the maximal dose of sacubitril with a less-than-maximal dose of enalapril. Secondly, sacubitril lowered blood pressure more than enalapril.

The angiotensin receptor blocker dose in sacubitril 200 mg is equivalent to valsartan 160 mg.[2] Accordingly, the angiotensin receptor blocker in sacubitril 200 mg twice daily is equivalent to the maximal dosage of valsartan approved by the US Food and Drug Administration. The dosage of enalapril in the PARADIGM-HF trial was 10 mg twice daily. While the target enalapril dosage for heart failure is 10 to 20 mg twice daily,[3] the dosage of enalapril in PARADIGM-HF was half the maximal approved dosage.

In the PARADIGM-HF trial, sacubitril 200 mg twice daily reduced the incidence of cardiovascular death by 19% compared with enalapril 10 mg twice daily (the rates were 16.5% vs 13.3%, respectively).[2] That sacubitril lowered mean systolic blood pressure 3.2 ± 0.4 mm Hg more than enalapril[2,4] may account for much of this benefit.

A 2002 study by Lewington et al[5] found that a 2-mm Hg decrease in systolic blood pressure reduces the risk of cardiovascular death by 7% in middle-aged adults. Granted, this study did not involve heart failure patients, but if its results are remotely applicable, a 3.2-mm Hg reduction in systolic blood pressure might be expected to reduce the rate of cardiovascular deaths by 10% to 11%.

Would sacubitril be superior to enalapril if the maximal dose of enalapril were compared to the maximal dose of sacubitril? Would sacubitril be superior to enalapril if blood pressure were lowered comparably between the two groups? These are relevant questions that the PARADIGM-HF trial fails to answer.

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IN REPLY: We thank Dr. Blankfield for raising these two important points. Although the findings of the PARADIGM-HF study are compelling, the design and results of this trial have incited many questions.

To address his first point, about the differential dosages of the two drugs, we agree, and we did mention in our review that one concern about the results of PARADIGM-HF is the unequal dosages of valsartan and enalapril in the two different arms. We mentioned that this dosage of enalapril was chosen based on its survival benefit in previous trials. However, this still raises the question of whether the benefit seen in the sacubitril-valsartan group was due to greater inhibition of the renin-angiotensin-aldosterone system rather than to the new drug.

To address his second point, the decrease in blood pressure in the sacubitril-valsartan arm was significant, and the patients taking this drug were more likely to have symptomatic hypotension, which may contribute to patient intolerance and difficulty initiating treatment with this drug. Dr. Blankfield brings up an interesting point regarding reduction of blood pressure driving the decrease of events in the sacubitril-valsartan group. In the original trial results section, the authors mentioned that when the difference in blood pressure between the two groups was examined as a time-dependent covariate, it was not a significant predictor of the benefit of sacubitril-valsartan.[1]

Furthermore, although higher blood pressure is associated with worse cardiovascular outcomes in the general population, higher blood pressure has been shown to be protective in heart failure patients.[2] Several studies have shown that the relationship between blood pressure and the mortality rate in patients with heart failure is paradoxical and complex.[2–4] Lee et al[3] found that this relationship was U-shaped, with increased mortality risk in those with high and low blood pressures (< 120 mm Hg). Ather et al[4] also showed that the relationship was U-shaped in patients with a mild to moderate reduction in left ventricular ejection fraction, but linear in those with severely reduced ejection fraction. This study also found that a decrease in systolic blood pressure below 110 mm Hg was associated with increased mortality risk.

The findings of PARADIGM-HF have sparked much conversation and implementation of practice change in the treatment of heart failure patients, and we await additional data on the use and limitations of sacubitril-valsartan in this group of patients.

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