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Reply: Sacubitril/valsartan for Chagas' heart disease heart failure?

Congratulations to Ramires *et al*. for the interest in Chagas' heart disease (CHD).[1] The CHD is a neglected disease, and all attention is welcome. [2,3] Based on an underpowered exploratory analysis of the PARADIGM-HF trial, the authors stated that sacubitril/valsartan arm had lower risk of experiencing cardiovascular death or heart failure (HF) hospitalization in comparison with enalapril arm. As pointed by the authors, the analysis results should be interpreted with caution. Also, a more detailed analysis of data presented by the authors showed a hazard ratio of 0.63 [95% confidence interval (CI): 0.31–1.28] for cardiovascular death or HF hospitalization; hazard ratio of 0.50 (95% CI: 0.20–1.26) for cardiovascular death, and hazard ratio of 0.83 (95% CI: 0.32–2.16) for HF hospitalization. Unexpectedly, the authors did not present data about the effect of sacubitril/valsartan on any cause of death, 'the king of hard endpoints'. Also, based on the characteristics of CHD HF population with reported lower systemic blood pressure and lower dose of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and beta-blockers in comparison with other aetiologies,[2] more data about safety profile of sacubitril/valsartan on CHD HF should be showed. More data about the hypotensive effect of sacubitril/valsartan in CHD HF may be justified because hypotension was found in 14% of the sacubitril/valsartan arm in the PARADIGM-HF trial. In addition, CHD HF is considered as an advanced form of HF,[4] and 75.9–74.3% of patients of the PARADIGM-HF trial were in New York Heart Association functional class I–II, therefore most in less severe forms of HF. In addition, more data about CHD HF patients excluded in the run-in period in the PARADIGM-HF trial are necessary to complement data about feasibility of sacubitril/valsartan in CHD HF. Lastly, it could be considered as an 'Achilles' heel' in the interpretation of PARADIGM-HF results on CHD HF the comparative design between enalapril and sacubitril/valsartan. Unfortunately, enalapril was never tested in large prospective double-randomized trials in CHF HF.[3] Some researchers could consider at least controversy the inclusion of CHD HF in comparative medication studies. Finally, at the same time that I would like to congratulate the authors for the importance of the data, I disagree with the statement that 'future trials should consider recruiting larger numbers of patients with CHD HF to allow adequately powered subgroup analysis'. In general, results of subgroup analysis are not conclusive and only generate hypothesis. In fact, we need specific future trials for CHD HF.[5] The CHF HF due to its relevance, high mortality, and typical characteristics (worse prognosis, persistent myocarditis, frequent right and left ventricular dysfunction, etc.)[6,7] warrants specific prospective double-blind large trials for treatment.[8]

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