Sacubitril/valsartan for patients with heart failure with preserved ejection fraction: what will the FDA decide?

To the editor Dr Lelonek's comprehensive review[1] of the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HFpEF) trial published in the December issue of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*) is particularly timely given that, at a public meeting on December 16, 2020, the United States Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee (CRDAC) voted 12 to 1 that the data presented supported the use of sacubitril/valsartan in the treatment of at least some patients with heart failure with preserved ejection fraction (HFpEF).[2] While, as Dr Lelonek notes, a modest overall benefit of borderline statistical significance was observed, there was a more substantial benefit in 2 prespecified subgroups: patients with a left ventricular ejection fraction (LVEF) at or below the median value of 57% and in women. The benefit of sacubitril/valsartan use in patients with a LVEF below the normal value, but not in the "reduced" range as currently defined (<40%), is biologically plausible and consistent with data for angiotensin receptor blockade and mineralocorticoid receptor antagonism.[3] Indeed, these data challenge the arbitrary LVEF cutoff points we use to define heart failure phenotypes and what we call those phenotypes. Recently, it has been suggested that the so-called heart failure with "mid-range" ejection fraction (HFmrEF) should be renamed to heart failure with "mildly reduced" ejection fraction (still HFmrEF!) to reflect the evidence that these patients seem to benefit from treatments that are clearly beneficial in patients with a more depressed LVEF, ie, in patients with left ventricular systolic dysfunction.[4] Indeed, should the CRDAC vote lead the FDA to approve sacubitril/valsartan for some patients with HFpEF, the LVEF range defining HFmrEF may also need to change. This is currently a LVEF of 40% to 49%, but the benefit of sacubitril/valsartan use appeared to extend to a higher LVEF. The findings in the 2 prespecified study subgroups may be related in that the benefit of sacubitril/valsartan use extended to a higher LVEF in women than in men, with qualitatively similar effects reported for angiotensin receptor blockade and mineralocorticoid receptor antagonism, suggesting that this is not a chance finding with sacubitril/valsartan.[3] It is well known that women have higher LVEFs on average than men and it is possible that women may still have left ventricular systolic dysfunction at a LVEF approaching to the normal value for men.

We must wait until later this year to hear what the FDA will decide about the use of sacubitril/valsartan in HFpEF. If their decision is positive, it will be not only good news for many patients but also an important stimulus for us to revisit our definition of what is a "normal" LVEF, how and why it differs between men and women, and what LVEF inclusion criteria we should use in future trials.

ARTICLE INFORMATION

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CONFLICT OF INTEREST JJVM reports employment by Glasgow University, honoraria for his work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, Dal-Cor, GSK, KBP Biosciences, Novartis, Pfizer, and Theracos, as well as personal honoraria from Abbott, Hikma, Ionis, Sun Pharmaceuticals, and Servier.

HOW TO CITE McMurray JJV. Sacubitril/valsartan for patients with heart failure with preserved ejection fraction: what will the FDA decide? Kardiol Pol. 2021; 79: 104-105. doi:10.33963/KP.15744

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3 Dewan P, Jackson A, Lam CSP, et al. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. Eur J Heart Fail. 2020; 22: 898-901.

4 Lam CSP, Voors AA, Ponikowski P, et al. Time to rename the middle child of heart failure: heart failure with mildly reduced ejection fraction. Eur Heart J. 2020; 41: 2353-2355.

Author's reply I appreciate the supporting commentary of Prof. John J. V. McMurray, the global leader and expert in heart failure. Time for heart failure with preserved ejection fraction (HFpEF) is particularly important now—it is a great chance for this population of patients to finally use the drug, sacubitril / valsartan, that has a beneficial effect on the prognosis of this disease.

The results of the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HFpEF) trial are also of great importance for the redefinition of the heart failure classification, as suggested by experts.[1] The last subanalyses of the trial also revealed the beneficial effect of angiotensin receptor-neprilysin inhibitors on the serum uric acid level, which was independently associated with an increased risk for primary outcomes (rate ratio, 1.61; 95% CI, 1.37–1.9)[2] and the beneficial effect on pulse pressure, a marker of arterial stiffness.[3] Last but not least, a 2020 analysis of PARAGON-HF trial data demonstrated that neprilysin could be a biological target in HFpEF with the decline of biomarkers reflecting extracellular matrix homeostasis.[4] Thus, it could be a mechanistic explanation for sacubitril / valsartan efficacy in HFpEF. However, further studies are needed to analyze the fibrotic signaling pathway in sacubitril / valsartan therapy.

ARTICLE INFORMATION

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CONFLICT OF INTEREST ML received consultation and lecture honoraria from Novartis and was the National Leader and Primary Investigator in the PARAGON-HF trial.

HOW TO CITE Lelonek M. Sacubitril / valsartan for patients with heart failure with preserved ejection fraction: what will the FDA decide? Author's reply. Kardiol Pol. 2021; 79: 105. doi:10.33963/KP.15745

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