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Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure

Recently, the Prospective Comparison of ARNI (angiotensin receptor–neprilysin inhibitor) with ARB (angiotensin receptor blocker) Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) trial suggested that women might obtain more benefit than men from sacubitril/valsartan, compared with valsartan, in heart failure with preserved ejection fraction (HFpEF).[1–3] However, the picture is more complicated as there was also an interaction between left ventricular ejection fraction (LVEF) and the effect of sacubitril/valsartan.[2] Patients with a LVEF at or below the median (57%) seemed to gain more benefit from sacubitril/valsartan than those with a LVEF above the median.[2] To make matters more complex still, it is well known that the distribution of LVEF is different in women and men, with women, on average, having a higher LVEF than men, be it in the general population or in individuals with heart failure (HF).[4–6] Despite a higher LVEF, women with HFpEF had worse systolic function, as assessed by tissue Doppler echocardiography, compared to men with HFpEF.[7] To further investigate the relationship between sex, LVEF and treatment in HF, we explored the effect of three different neurohumoral modulators in large trials which provide data on clinical outcomes in patients with HF, across the full range of LVEF, incorporating the three commonly described HF phenotypes – HF with reduced ejection fraction (HFrEF, LVEF <40%), HFpEF (LVEF >50%) and HF with mid-range ejection fraction (HFmrEF, LVEF 40–50%).[8]

We pooled individual patient-level data from: (i) three trials using an angiotensin receptor blocker – the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) – the CHARM-Alternative and CHARM-Added trials in HFrEF and the CHARM-Preserved trial in HFmrEF/HFpEF;[9] (ii) three trials using a mineralocorticoid receptor antagonist (MRA) – two HFrEF trials, the Randomized Aldactone Evaluation Study (RALES) and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), and one HFmrEF/HFpEF trial – the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT).[10–12] Only TOPCAT patients from the Americas were included; (iii) two trials using sacubitril/valsartan – the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF trial (PARADIGM-HF) in HFrEF and PARAGON-HF in HFmrEF/HFpEF.[1,13]

Cox proportional hazards modelling was used to analyse (i) the primary composite outcome (first occurrence of HF hospitalization or cardiovascular death); (ii) first HF hospitalization; and (iii) cardiovascular death. Likelihood ratio tests were used to report (i) two-way interaction between treatment and sex; and (ii) three-way interaction between treatment, sex and LVEF. LVEF, modelled as a fractional polynomial, and its interaction with treatment using the best fit model for each drug category (based on the primary composite outcome) was examined with the mfpi command in Stata. Models were stratified by trial for MRAs and sacubitril/valsartan. All analyses were conducted using Stata version 16 (Stata Corp., College Station, TX, USA).

This present analysis included 2400, 1938 and 4311 women and 5199, 4229 and 8884 men in the candesartan, MRA and sacubitril/valsartan trials, respectively (*Table 1*). Overall mean LVEF (%) was $38.9 \pm 14.9\%$, $35.3 \pm 16.0\%$ and $39.7 \pm 15.1\%$, respectively. Women had a higher mean LVEF, with the difference compared to men 6.3%, 9.4% and 10.3%, respectively. Women had a lower incidence of the primary composite outcome (and its components) in each of the treatment and control groups.

In keeping with prior reports from the CHARM Programme and TOPCAT, as well as a recent analysis of PARADIGM-HF and PARAGON-HF, we found that treatment with an ARB, MRA or ARNI may be of benefit beyond the upper limit of LVEF eligibility used in contemporary HFrEF clinical trials (40%) and may extend to what has been termed HFmrEF (LVEF 40–49%) and even to the lower part of the LVEF range currently categorized as HFpEF.[2,6,14,15] Importantly, the benefit of each treatment seemed to extend to a higher LVEF in women, compared to men (*Figure 1*). There was no difference in efficacy of therapy between men and women with HFrEF.

Because these are *post hoc* analyses, they are only hypothesis generating. However, the fact that all three neurohumoral modulating therapies demonstrated the same sex-related pattern of response raises the possibility that the differential response between women and men identified in PARAGON-HF may be real rather than due to the play of chance, although interpretation of PARAGON-HF is more complex as it had an active comparator compared with a placebo control in the other trials. Despite this consistent observation in the trials examined, the biological basis for such a finding is uncertain. As detailed elsewhere, the possibilities include sex-related differences in cardiac remodelling in response to blood pressure, age and other stimuli, and differences in age-related arterial stiffening, which is more pronounced in women than men.[3] Women may also have other evidence of contractile dysfunction, compared with men, for a given ejection fraction.[3] Natriuretic peptide levels are lower in women with HFpEF than in men, and women may have reduced cyclic guanosine monophosphate-protein kinase G signalling compared with men, especially after the menopause.[3] The possibility that women with HF might benefit from treatment to a higher level of LVEF than previously considered could be of great clinical importance. Women with HF have fewer treatment options than men with HF because HFmrEF and HFpEF are the predominant HF phenotypes in women and no therapy has been approved by regulatory authorities for either of these phenotypes.[6] More research on this matter is clearly required.

Conflict of interest: P.D. and A.J. report no conflicts. C.S.P.L., M.A.P., F.Z., B.P., S.D.S. and J.J.V.McM. or their institutions were paid for their participation in one or more of these trials. J.J.V.McM reports receiving fees (all fees listed paid

Table 1 Interaction of treatment and left ventricular ejection fraction in men and women with heart failure

	Overall	Men	Women	*P*-interaction[a]	*P*-interaction[b]	*P*-interaction[c]
Candesartan						
Patients, *n*	7599	5199	2400			
Age, years, mean ± SD	65.5 ± 11.1	64.4 ± 10.9	67.8 ± 11.1			
Ejection fraction, %, mean ± SD	38.9 ± 14.9	36.9 ± 14.0	43.2 ± 15.8			
Primary composite outcome						
Event rate per 100 pt. years (95% CI)						
Placebo	13.8 (13.1–14.6)	14.3 (13.4–15.2)	12.9 (11.7–14.3)			
Candesartan	11.6 (10.9–12.2)	11.9 (11.1–12.7)	10.8 (9.7–12.0)			
Hazard ratio (95% CI)	0.84 (0.78–0.91) <0.001	0.84 (0.76–0.92)	0.84 (0.73–0.97)	0.9939	0.0146	0.0649
HF hospitalization						
Event rate per 100 pt. years (95% CI)						
Placebo	9.7 (9.1–10.3)	9.7 (9.0–10.5)	9.6 (8.6–10.8)			
Candesartan	7.6 (7.1–8.2)	7.6 (7.0–8.3)	7.5 (6.6–8.6)			
Hazard ratio (95% CI)	0.79 (0.72–0.87) <0.001	0.79 (0.70–0.89)	0.79 (0.66–0.94)	0.9824	0.0566	0.1361
Cardiovascular death						
Event rate per 100 pt. years (95% CI)						
Placebo	7.2 (6.7–7.7)	7.6 (7.0–8.3)	6.3 (5.5–7.2)			
Candesartan	6.3 (5.9–6.8)	6.7 (6.2–7.4)	5.4 (4.7–6.2)			
Hazard ratio (95% CI)	0.88 (0.79–0.97) 0.013	0.89 (0.79–1.00)	0.86 (0.70–1.04)	0.7531	0.3454	0.1876
MRA						
Patients, *n*	6167	4229	1938			
Age, years, mean ± SD	68.5 ± 9.8	67.8 ± 9.6	70.1 ± 10.1			
Ejection fraction, %, mean ± SD	35.3 ± 16.0	32.3 ± 14.0	41.7 ± 18.1			
Primary composite outcome						
Event rate per 100 pt. years (95% CI)						
Placebo	20.0 (18.8–21.2)	21.7 (20.2–23.3)	16.8 (15.0–18.7)			
MRA	14.0 (13.1–15.0)	15.2 (14.0–16.4)	11.8 (10.5–13.4)			
Hazard ratio (95% CI)	0.70 (0.64–0.77) <0.001	0.70 (0.63–0.77)	0.71 (0.60–0.84)	0.8089	0.0074	0.0682
HF hospitalization						
Event rate per 100 pt. years (95% CI)						
Placebo	13.9 (13.0–14.9)	14.8 (13.5–16.1)	12.3 (10.9–14.0)			
MRA	9.4 (8.7–10.2)	9.9 (9.0–11.0)	8.4 (7.3–9.8)			
Hazard ratio (95% CI)	0.69 (0.62–0.77) <0.001	0.68 (0.60–0.78)	0.70 (0.57–0.85)	0.8567	0.0077	0.1006
Cardiovascular death						
Event rate per 100 pt. years (95% CI)						
Placebo	9.7 (9.0–10.5)	10.8 (9.8–11.8)	7.6 (6.6–8.9)			
MRA	7.0 (6.4–7.7)	8.1 (7.3–9.0)	5.1 (4.2–6.1)			
Hazard ratio (95% CI)	0.73 (0.65–0.82) <0.001	0.75 (0.65–0.86)	0.67 (0.53–0.84)	0.4100	0.9333	0.9494
Sacubitril/valsartan						
Patients, *n*	13 195	8884	4311			
Age, years, mean ± SD	67.0 ± 11.3	65.6 ± 11.3	70.0 ± 10.6			
Ejection fraction, %, mean ± SD	39.7 ± 15.1	36.3 ± 13.4	46.6 ± 16.0			
Primary composite outcome						
Event rate per 100 pt. years (95% CI)						
RAAS inhibitor	11.4 (10.8–11.9)	12.3 (11.6–13.0)	9.6 (8.8–10.5)			
Sacubitril/valsartan	9.5 (9.1–10.0)	10.6 (9.9–11.2)	7.6 (6.9–8.4)			
Hazard ratio (95% CI)	0.84 (0.78–0.90) <0.001	0.86 (0.79–0.93)	0.79 (0.70–0.91)	0.3452	*0.0424*	0.0034
HF hospitalization						
Event rate per 100 pt. years (95% CI)						
RAAS inhibitor	7.4 (7.0–7.9)	7.6 (7.1–8.2)	7.0 (6.3–7.8)			
Sacubitril/valsartan	6.2 (5.9–6.6)	6.7 (6.2–7.3)	5.3 (4.7–5.9)			
Hazard ratio (95% CI)	0.84 (0.77–0.92) <0.001	0.89 (0.80–0.98)	0.76 (0.65–0.88)	0.1003	0.0560	0.0057
Cardiovascular death						
Event rate per 100 pt. years (95% CI)						
RAAS inhibitor	5.6 (5.3–6.0)	6.6 (6.1–7.1)	3.8 (3.3–4.3)			
Sacubitril/valsartan	4.7 (4.4–5.0)	5.4 (5.0–5.9)	3.3 (2.9–3.8)			
Hazard ratio (95% CI)	0.83 (0.76–0.92) <0.001	0.81 (0.73–0.91)	0.89 (0.73–1.08)	0.4461	0.2136	0.5871

CI, confidence interval; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RAAS, renin–angiotensin–aldosterone system; SD, standard deviation.
Hazard ratios were stratified for trial in case of MRA and sacubitril/valsartan.
[a]Interaction between treatment and sex.
[b]Interaction between treatment and ejection fraction modelled as a fractional polynomial.
[c]Three-way interaction between treatment, sex and ejection fraction.

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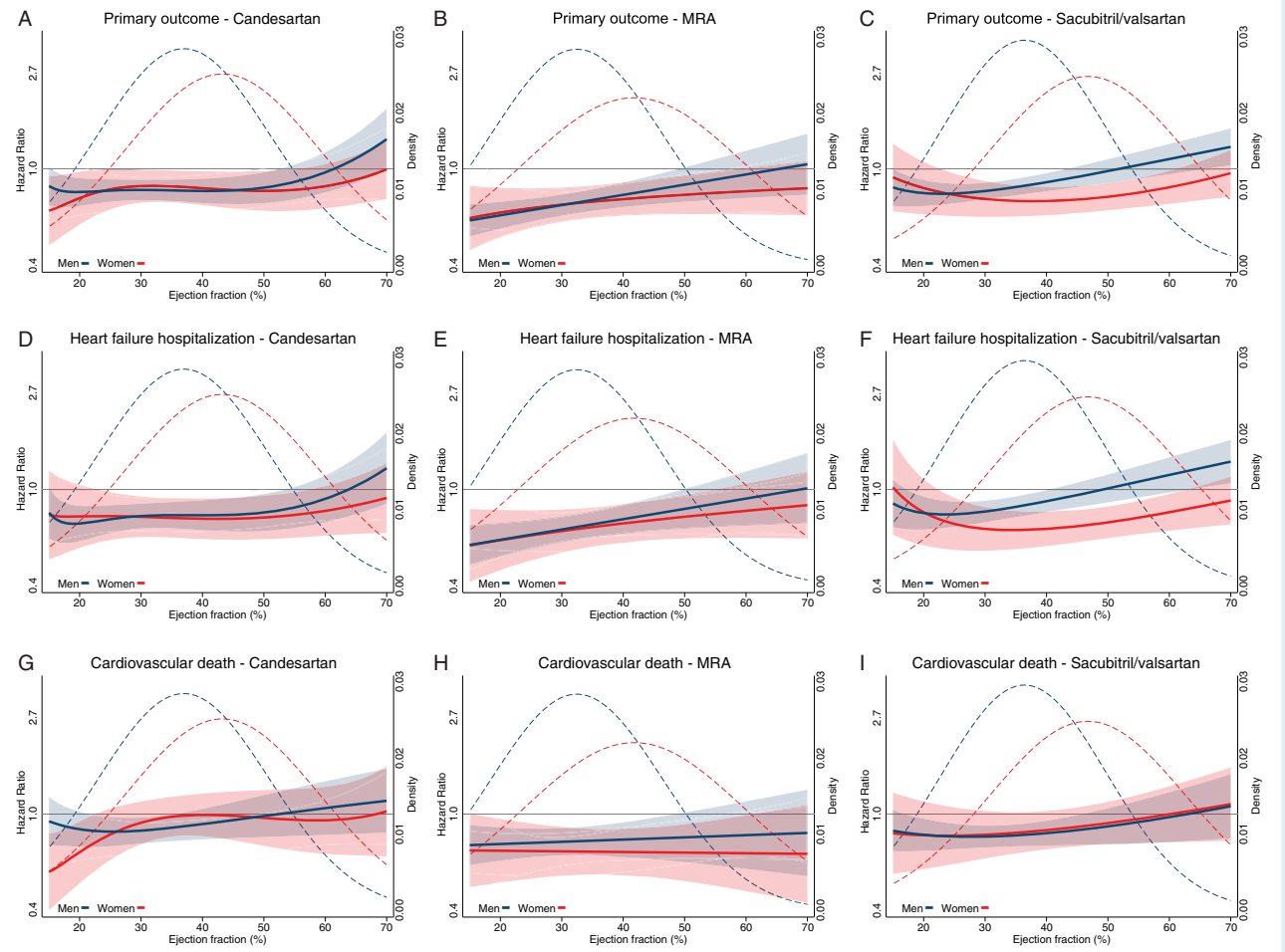

Figure 1 Variation of treatment effect with left ventricular ejection fraction in heart failure. Dotted curves show normalized distribution of left ventricular ejection fraction (LVEF) in men and women. Solid lines show a continuous hazard ratio for the primary composite and its components, according to treatment group in the range of LVEF included. The shaded areas represent the 95% confidence intervals. Primary outcome (heart failure hospitalization/cardiovascular death): (*A*) candesartan vs. placebo; (*B*) mineralocorticoid receptor antagonist (MRA) vs. placebo; (*C*) sacubitril/valsartan vs. renin–angiotensin–aldosterone system inhibitor. Heart failure hospitalization: (*D*) candesartan vs. placebo; (*E*) MRA vs. placebo; (*F*) sacubitril/valsartan vs. renin–angiotensin–aldosterone system inhibitor. Cardiovascular death; (*G*) candesartan vs. placebo; (*H*) MRA vs. placebo; (*I*) sacubitril/valsartan vs. renin–angiotensin–aldosterone system inhibitor.

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Eplerenone prevents an increase in serum carboxy-terminal propeptide of procollagen type I after myocardial infarction complicated by left ventricular dysfunction and/or heart failure

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), eplerenone reduced morbidity and mortality in patients who had an acute myocardial infarction (MI), complicated by systolic dysfunction, heart failure (HF) or diabetes mellitus.[1] In a prespecified secondary analysis of EPHESUS, Iraqi *et al.*[2] reported concomitant reductions in the serum concentrations of N-terminal propeptide of type I (PINP) and type III (PIIINP) collagen, which may reflect an antifibrotic effect of eplerenone; however, the carboxy-terminal propeptide of procollagen type I (PICP) was not analysed in that report. Studies of endomyocardial biopsies suggest that serum PIIINP and PICP (but not PINP fragments) reflect myocardial fibrosis.[3] Moreover, PICP originates directly from the synthesis of collagen type I in a 1:1 ratio, directly reflecting collagen type I synthesis. On the other hand, PIIINP originates from partially processed procollagen molecules on the surface of collagen type III fibres. Therefore, serum PIIINP may not accurately reflect ongoing collagen type III synthesis. Furthermore, a net release from the heart into the circulation has only been reported for PICP (and not for PIIINP).[4] Notwithstanding, for no good reason, trials of mineralocorticoid receptor antagonists (MRAs) have focused more on PIIINP than on PICP.

The type of collagen as well as the amount may be an important determinant of its effects on myocardial function. Collagen type I comprises highly cross-linked, large-diameter fibres that have a major impact on stiffness whereas collagen type III comprises mainly non-cross-linked, small-diameter, more pliable fibres.[3] Whether eplerenone also reduces serum PICP has not been reported thus far.