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

Authors:

Pooja Dewan MBBS[1]

Alice Jackson MBChB[1]

Carolyn S.P. Lam MBBS PhD[2,3,4]

Marc A. Pfeffer MD PhD[5]

Faiez Zannad MD PhD[6]

Bertram Pitt MD[7]

Scott D. Solomon MD[5]

John J.V. McMurray MD[1]

Affiliations:

[1]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [2]National Heart Center Singapore and Duke–National University of Singapore, Singapore; [3]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [4]The George Institute for Global Health, Australia; [5]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston; [6]INSERM

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CIC 1433 NI-CRCT (Cardiovascular and Renal Clinical Trialists) F-CRIN network Université de Lorraine and CHRU Nancy France;

[7]Division of Cardiology, University of Michigan, Ann Arbor, MI.

Corresponding author: Professor John J.V. McMurray,

British Heart Foundation Cardiovascular Research Centre,

University of Glasgow,

126 University Place,

Glasgow, G12 8TA,

United Kingdom.

Tel: +44 141 330 3479

Fax: +44 141 330 6955

Email: john.mcmurray@glasgow.ac.uk

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Recently, the Prospective comparison of ARni (Angiotensin receptor-neprilysin inhibitor) with Arb (angiotensin receptor blocker) Global Outcomes in heart failure (HF) with preserved ejectioN fraction trial (PARAGON-HF) suggested that women might obtain more benefit than men from sacubitril/valsartan, compared with valsartan, in HF 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 than sacubitril/valsartan 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.[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%), HF with preserved ejection fraction (HFpEF – LVEF >50%) and HF with mid-range ejection fraction (HFmrEF - LVEF 40-50%).[8]

We pooled individual patient-level data from: 1) 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] 2) Three trials using a mineralocorticoid receptor antagonist (MRAs) – two HFrEF trials, the Randomised Aldactone Evaluation Study (RALES), Eplerenone in Mild Patients Hospitalization and Survival Study in HF trial (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. 3) 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 interactions 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 ver.16.

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±14.9, 35.3±16.0 and 39.7±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 Program and TOPCAT, as well as a recent analysis of PARADIGM-HF and PARAGON-HF, we found that 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 (cGMP)-protein kinase G (PKG) 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.

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

	Overall	Men	Women	p-interaction*	p-interaction$	p-interaction#
Candesartan						
Number of patients	*7599*	5199	2400			
Age – 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. yrs. (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. yrs. (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. yrs. (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
Mineralocorticoid receptor blocker (MRA)							
Number of patients		*6167*	4229	1938			
Age – 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 outcome							
Event rate per 100 pt. yrs. (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. yrs. (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. yrs. (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							
Number of patients		*13195*	8884	4311			
Age – 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 outcome							
Event rate per 100 pt. yrs. (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. yrs. (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. yrs. (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

*Interaction between treatment and sex.
$Interaction between treatment and ejection fraction modelled as a fractional polynomial.

[#]Three-way interaction between treatment, sex and ejection fraction.
Hazard ratios were stratified for trial in case of MRAs and sacubitril-valsartan.

Figure legend

Figure 1: Variation of treatment effect with left ventricular ejection fraction in heart failure.

Dotted curves show normalized distribution of LVEF in men (blue) and women (red). Solid blue (men) and red (women) lines show a continuous hazard ratio for the primary composite and its components, according to treatment group the range of LVEF included. The shaded areas represent the 95% confidence intervals:

Primary outcome (HF hospitalization/cardiovascular death)

A) candesartan vs placebo

B) MRA vs placebo

C) sacubitril-valsartan vs RAAS inhibitor.

Heart failure hospitalization

D) candesartan vs placebo

E) MRA vs placebo

F) sacubitril-valsartan vs RAAS inhibitor

Cardiovascular death

G) candesartan vs placebo

H) MRA vs placebo

I) sacubitril-valsartan vs RAAS inhibitor