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Relationship of serum sodium concentration to mortality in a wide spectrum of heart failure patients with preserved and with reduced ejection fraction: an individual patient data meta-analysis†

Meta-Analysis Global Group in Chronic heart failure (MAGGIC)

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Aims Hyponatraemia has been associated with reduced survival in patients with heart failure and reduced ejection fraction (HF-REF). The relationship between serum sodium and outcome is unclear in heart failure with preserved (≥50%) ejection fraction (HF-PEF). Therefore, we used a large individual patient data meta-analysis to study the risk of death associated with hyponatraemia in HF-REF and in HF-PEF.

Methods and results This analysis included 14 766 patients from 22 studies that recruited patients without ejection fraction inclusion criterion at baseline and reported death from any cause. Cox proportional analysis was undertaken for hyponatraemia (sodium <135 mmol/L), adjusted for variables of clinical relevance, and stratified by study. The endpoint was death from any cause at 3 years. Patients with hyponatraemia ($n = 1618$) and patients with normal serum sodium had similar characteristics as regards to age, gender, and ischaemic aetiology. However, patients with hyponatraemia had higher New York Heart Association class and lower blood pressure. At follow-up, there were 335 deaths among 1618 patients with hyponatraemia (21%) and 2128 deaths among 13 148 patients with normal serum sodium (16%). The risk of death appeared to increase linearly with serum sodium levels <140 mmol/L. Hyponatraemia was identified in 1199 HF-REF patients (11%) and 419 HF-PEF patients (11%). Hyponatraemia was independently predictive of death in both HF-REF [adjusted hazard ratio (HR) 1.69, 95% confidence interval (CI) 1.50–1.91] and HF-PEF (adjusted HR 1.40, 95% CI 1.10–1.79, *P* for interaction 0.20).

Conclusion Hyponatraemia is a powerful determinant of mortality in patients with HF regardless of ejection fraction. Further work is needed to determine if correction of hyponatraemia translates into clinical benefit.

Keywords Heart failure • Ejection fraction • Sodium • Prognosis • Meta-analysis

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Introduction

Hyponatraemia (usually defined as a serum sodium concentration <135 mmol/L)[1] is observed in ~ 20% of patients admitted to hospital for heart failure (HF).[2–4] Studies conducted in various patient populations of chronic and acutely decompensated HF have shown an association between low serum sodium concentration and poor prognosis.[2–7] Most of these studies were focused on short-term outcomes.[2–4] Risk models developed in different HF cohorts of outpatients[8,9] and hospitalized patients[10–12] have suggested that hyponatraemia is one of the most powerful predictors of mortality in HF. Few studies that investigated the relationship between serum sodium concentration and outcome have included patients with heart failure and preserved ejection fraction (HF-PEF).[2,9,12–14] It is now clear that HF-PEF accounts for a substantial proportion of cases of HF[15,16] and has distinct features compared with heart failure with reduced ejection fraction (HF-REF).[16] The prognostic role of hyponatraemia has not been well investigated in HF-PEF. Despite an increasing awareness of the prognostic role of hyponatraemia in HF, treatment strategies remain elusive and, in recent clinical trials, vasopressin receptor antagonists did not reduce mortality.[17,18]

To overcome the limitations of the previous studies, we combined in the present meta-analysis individual patient data from a large number of studies [observational studies and randomized clinical trials (RCTs)] with long follow-up and a large number of clinical events. Our primary hypothesis was that hyponatraemia is independently predictive of outcome in both HF-REF and HF-PEF.

Methods

The design of the Meta-Analysis Global Group in Chronic heart failure (MAGGIC) meta-analysis was described previously.[16] We undertook a comprehensive literature-based meta-analysis of observational studies and RCTs published to the end of 2008. In brief, we searched online databases including Embase, Medline, Medline In-progress, and PubMed using the key words: prognosis, outcome, heart failure, left ventricle, and preserved. We also searched reference lists of articles obtained during the search and conference abstracts, and made personal contact with the investigators and authors. Abstracts, unpublished studies, and articles published in languages other than English were not excluded. Eligible studies were those that included patients with HF without left ventricular ejection fraction (LVEF) entry criterion and reported death from any cause. We identified 56 potentially suitable studies, the principal investigators of which were invited to participate in the meta-analysis. Investigators (see Appendix) from 30 studies (two pharmacotherapy RCTs, four management intervention RCTs, and 24 observational studies) provided individual patient data on a predefined set of variables including demographics, medical history, medical treatment, symptom status, clinical variables, laboratory variables, and outcome (all-cause mortality and duration of follow-up). Data from the individual studies were re-coded at the Coordinating Centre at the University of Auckland into a uniform format, checked, and finally incorporated into one database. The data set included patients who were seen for a baseline assessment either at an outpatient visit or at the time of a hospital admission. However, for those studies that recruited patients during an admission, we have excluded those patients who died during the index admission. The present analysis included 22 studies that provided serum sodium concentration (14 766 patients). Preserved LVEF was pre-specified as LVEF ≥ 50%.[16] Serum sodium was available from the baseline assessment in each of these studies, either at an outpatient visit or at discharge from hospital. Hyponatraemia was defined as a serum sodium concentration <135 mmol/L.[1]

Individual studies were approved by Ethics Committees. The meta-analysis complies with the Declaration of Helsinki and was approved by The University of Auckland Human Subjects Ethics Committee. The corresponding author had final responsibility for the decision to submit the manuscript. All authors have read and agreed to the manuscript as written.

Statistical analysis

The baseline continuous variables were compared by the use of the Student's *t*-test. The χ^2 test of proportions was used for categorical variables. For all analyses, the outcome was the rate of death from any cause at 3 years from hospital discharge or after the baseline study visit. Survival analyses used Cox proportional hazard models with serum sodium as a continuous and categorical variable (<135 mmol/L and ≥ 135mmol/L). Cox models were stratified by study and adjusted for age, gender, ejection fraction group, hypertension, diabetes, atrial fibrillation, and ischaemic aetiology. These variables chosen for the model were selected for clinical relevance and each was available in > 90% of the patients in the data set. Estimated glomerular filtration rate (eGFR) was available in fewer patients. However, due to its importance in relation to the outcome, the multivariable models were re-run after incorporation of this variable into the above model. The correlation between the scaled Schoenfeld residuals and the length of follow-up showed that there was no violation of the proportional hazards assumption for all analyses. Mortality curves were derived from adjusted models.

The relationship between serum sodium concentration and the risk of death from any cause at 3 years was also explored using spline fits. For the purpose of deriving informative risk estimates, sodium levels ≤ 130 mmol/L or ≥ 146 mmol/L were pooled (due to relatively small subject numbers outside these values). Cox proportional hazards models were constructed for the risk of death from any cause with a sodium concentration of 135 mmol/L as referent. Models were adjusted for age, gender, hypertension, ischaemic aetiology, atrial fibrillation, and diabetes, and stratified by study. The Transreg procedure of SAS (v9.2) was used to fit spline piecewise polynomials using the b-spline algorithm. Models were empirically chosen from inspection of the plots firstly with knots at 137, 140, and 142 mmol/L (quartiles of the sodium concentration distribution), secondly with a knot at 140 mmol/L, and, finally, with a knot at 135 mmol/L. Confidence intervals (CIs) and prediction intervals were inspected for the plots and the residuals considered. Parsimony and goodness of fit formed the basis of model choice, and models were checked for convergence. Analyses were performed using R version 2.9.0 and SAS version 9.2.

Results

Baseline characteristics

Data on serum sodium concentration were available for 14 766 patients from 22 studies. Patients included in the MAGGIC meta-analysis had a wide distribution of serum sodium levels (*Figure 1*). Median LVEF was 36% [interquartile range (IQR) 26–48]. Eleven per cent of patients had serum sodium <135 mmol/L. The baseline characteristics of patients according to the presence

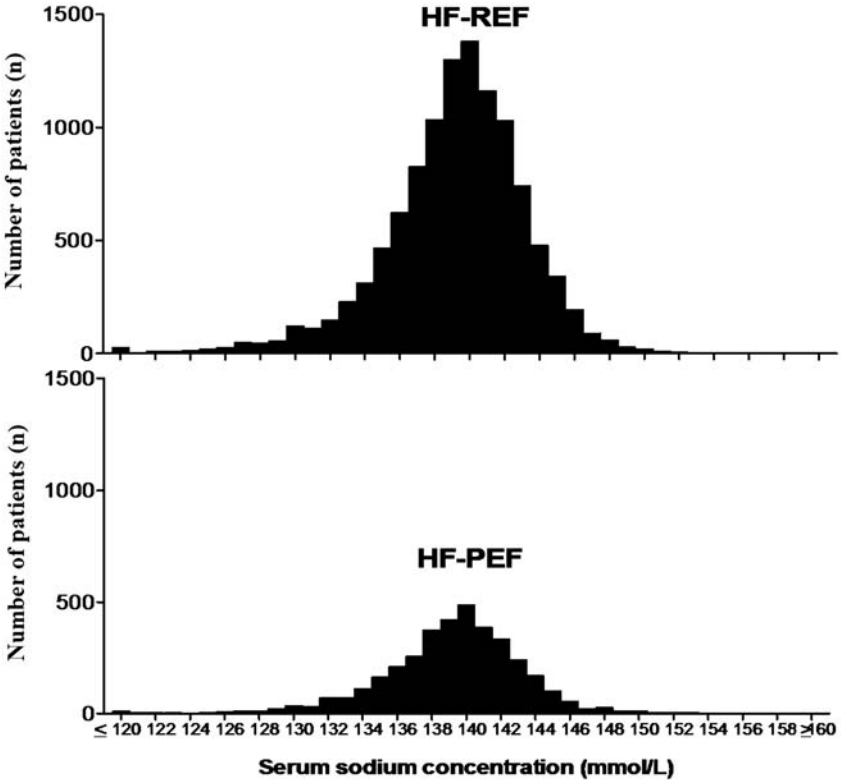

Figure 1 Distribution of serum sodium concentration in patients with heart failure and reduced ejection fraction (HF-REF) and in patients with heart failure and preserved ejection fraction (HF-PEF).

or absence of hyponatraemia (defined as serum sodium concentration <135 mmol/L) are described in *Table 1*. Patients with hyponatraemia ($n = 1618$) were older, more frequently had diabetes mellitus and atrial fibrillation, and had worse clinical status [greater New York Heart Association (NYHA) class, lower systolic and diastolic blood pressure, and higher heart rate] than patients without hyponatraemia ($n = 13\ 148$) (*Table 1*). Mean LVEF was similar in both groups. As regards to medical therapy, patients with hyponatraemia were more often treated with diuretics, whereas angiotensin-convering enzyme inhibitors/angiotensin receptor blockers and beta-blockers were prescribed more frequently in patients with normal sodium levels (*Table 1*). Information on prior revascularization was found in the overall cohort in 10 964 patients (74%). Of these, 269 (21%) patients with hyponatraemia had been previously revascularized and 2057 (21%) patients without hyponatraemia had been revascularized

Table 2 describes the baseline characteristics of patients with low serum sodium compared with patients without hyponatraemia, separately for the HF-PEF and HF-REF groups. HF-PEF patients with hyponatraemia were older, had a more severe clinical profile, and less angiotensin-convering enzyme inhibitor/angiotensin receptor blocker and beta-blocker therapy compared with HF-PEF patients with normal sodium levels (*Table 2*). HF-REF patients with low serum sodium concentration more often had diabetes and previous atrial fibrillation, lower LVEF, more severe clinical forms of HF, and lower prescribed rates of evidence-based HF drugs compared with HF-REF patients without hyponatraemia (*Table 2*). The proportion of patients with hyponatraemia in the two groups (HF-PEF and HF-REF) was identical: 11%.

Outcome

At follow-up, there were 335 deaths among 1618 patients (21%) with hyponatraemia and 2128 deaths among 13 148 patients (16%) without hyponatraemia. Median follow-up was 365 days (IQR 91–1096) in the overall cohort, 198 days (IQR 86–1096) in the HF-PEF group, and 365 days (IQR 94–1096) in the HF-REF group.

When serum sodium concentration was analysed as a continuous variable in the overall cohort, we found a linear increase in the risk of all-cause mortality at 3 years at concentrations <140 mmol/L, and a plateau at concentrations ≥ 140 mmol/L (*Figure 2*).

In a Cox proportional hazard model adjusted for age and gender (*Table 3*), patients with hyponatraemia were at higher risk of death than patients with normal serum sodium [adjusted hazard ratio (HR) 1.64, 95% CI 1.48–1.81], and this relationship was observed for patients with HF-REF (adjusted HR 1.72, 95% CI 1.53–1.93), and for patients with HF-PEF (adjusted HR 1.36, 95% CI 1.08–1.72). There was no interaction between LVEF and outcome prediction of hyponatraemia (*P* for interaction 0.20). After adjustment

Table 1 Baseline characteristics of patients according to the presence or absence of hyponatraemia

	Hyponatraemia		*P*-value
	No	Yes	
n (22 studies)	13 148	1618	
Age, years (SD)	68 (12)	69 (13)	0.0073
Women, %	35	37	0.078
Medical history			
Hypertension, %	45	45	0.93
Myocardial infarction, %	40	37	0.0056
Atrial fibrillation, %	21	25	0.0004
Diabetes mellitus, %	23	30	<0.0001
Ischaemic aetiology, %	56	55	0.22
Medication			
ACE inhibitor or ARB, %	83	77	<0.0001
Beta-blocker, %	37	31	<0.0001
Loop diuretic, %	81	84	0.0002
Spironolactone, %	20	33	<0.0001
Digoxin, %	39	40	0.25
Clinical status			
NYHA class (I/II/III/IV), %	16/45/30/9	16/34/34/16	<0.0001
Heart rate, b.p.m. (SD)	80 (20)	84 (21)	<0.0001
SBP, mmHg (SD)	134 (26)	127 (27)	<0.0001
DBP, mmHg (SD)	78 (15)	75 (14)	<0.0001
LVEF, %, median (IQR)	36 (27–49)	35 (25–49)	0.042

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

for age, gender, ejection fraction group, atrial fibrillation, hypertension, ischaemic aetiology, and diabetes, and stratification by study (*Table 3*), hyponatraemia remained a strong independent predictor of mortality (adjusted HR 1.64, 95% CI 1.47–1.82 for the whole group; adjusted HR 1.69, 95% CI 1.50–1.91 for HF-REF; and adjusted HR 1.40, 95% CI 1.10–1.79 for HF-PEF). Mortality for patients with HF-REF and for patients with HF-PEF according to the presence or absence of hyponatraemia is displayed in *Figure 3*.

Further adjustment for eGFR (11 954 patients with available eGFR: 8966 with HF-REF and 2988 with HF-PEF) did not influence the relationship between low serum sodium and mortality (*Table 3*). Hyponatraemia remained independently predictive of death from any cause in the overall cohort (adjusted HR 1.60, 95% CI 1.43–1.78), in patients with HF-REF (adjusted HR 1.64, 95% CI 1.45–1.86), and in patients with HF-PEF (adjusted HR 1.35, 95% CI 1.06–1.72).

Analysis of the risk of death from any cause by LVEF category (*Figure 4*) showed increased risk of death associated with hyponatraemia for moderately reduced LVEF as well as for severely reduced LVEF.

Discussion

This study resulting from a large individual patient data meta-analysis demonstrates that serum sodium concentration has a strong influence on long-term outcome in a wide spectrum of HF patients with reduced and with preserved LVEF. Patients with hyponatraemia generally have more severe clinical forms of HF and are less often treated with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers. The risk of all-cause death associated with hyponatraemia (defined as a serum sodium concentration <135 mmol/L) is substantial. Moreover, the excess long-term mortality associated with hyponatraemia is observed even after adjusting for other major prognostic variables and is independent of LVEF. Finally, the shape of the relationship between serum sodium concentration and risk of death suggests that mortality may increase within the 'standard' reference limits of 135–140 mmol/L compared with levels ≥ 140 mmol/L.

Hyponatraemia is observed in 18–30% of patients admitted to hospital for HF.[2–4,19,20] The prevalence seems to be lower in outpatients with chronic HF.[21] The current data from the MAGGIC meta-analysis show lower prevalence of hyponatraemia, as compared with previous studies conducted in acute HF. This lower prevalence of hyponatraemia in our analysis might be due to the fact that all patients in the MAGGIC cohort were out of hospital at the time of the baseline data (for the studies that recruited patients during an admission we have excluded patients who died during the index admission). According to our results, the prevalence of hyponatraemia is identical in patients with HF-REF and in patients with HF-PEF. In both groups (HF-REF and HF-PEF), hyponatraemia is associated with more severe clinical features and less intensive medical therapy. Patients with HF-PEF and hyponatraemia are older, whereas patients with HF-REF and low serum sodium are more often diabetics with previous atrial fibrillation.

In HF, hyponatraemia results from a non-osmotically mediated increase in arginine vasopressin (AVP) levels in response to arterial underfilling.[22] Stimulation of V_{1a} receptors of the vascular bed results in increased vascular resistance, while stimulation of the V_2 receptors in the collecting ducts of the nephron leads to increased water reabsorbtion and dilutional hyponatraemia.[23] While in normal physiological states, changes in plasma osmolarity precede changes in volume in controlling AVP release, this mechanism does not hold in HF.[24] Non-osmotic release of AVP by HF-mediated activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system leads to persistent renal water reabsorbtion despite a low plasma osmolarity. It is still unclear whether low serum sodium is merely a marker of a more advanced underlying disease or if there is a direct association between the sodium abnormality and reduced survival.

Hyponatraemia has been demonstrated to be an important predictor of outcome in outpatients with HF[8,9,21] and in patients admitted to hospital for acute HF.[2–4,6,10–14] Secondary analyses of RCTs have linked hyponatraemia to greater in-hospital mortality and a higher short-term death/rehospitalization rate.[3,4,25] In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry,[2] patients with low serum sodium concentration hospitalized for acute HF had

Table 2 Baseline characteristics of patients with HF-PEF and patients with HF-REF according to the presence or absence of hyponatraemia

	HF-PEF (n = 3737)			HF-REF (n = 11 029)		
	Hyponatraemia		*P*-value	Hyponatraemia		*P*-value
	No	Yes		No	Yes	
N (22 studies)	3318 (89%)	419 (11%)		9830 (89%)	1199 (11%)	
Age, years (SD)	70 (12)	73 (12)	<0.0001	67 (12)	67 (13)	0.47
Women, %	53	57	0.11	29	30	0.35
Medical history						
Hypertension, %	60	61	0.58	42	40	0.75
Myocardial infarction, %	25	22	0.097	45	42	0.029
Atrial fibrillation, %	24	25	0.62	20	25	<0.0001
Diabetes mellitus, %	25	29	0.092	22	30	<0.0001
Ischaemic aetiology, %	49	44	0.053	59	58	0.8
Medication						
ACE inhibitor or ARB, %	68	60	<0.0001	88	82	0.0002
Beta-blocker, %	37	30	0.0072	37	32	0.0006
Loop diuretic, %	79	82	0.095	81	85	0.0007
Spironolactone, %	15	24	<0.0001	22	37	<0.0001
Digoxin, %	28	26	0.45	43	45	0.067
Clinical status						
NYHA class (I/II/III/IV), %	25/45/23/7	25/35/23/17	0.0028	13/46/32/9	13/34/37/16	<0.0001
Heart rate, b.p.m. (SD)	79 (21)	84 (20)	0.001	80 (20)	84 (21)	<0.0001
SBP, mmHg (SD)	143 (28)	140 (29)	0.12	130 (25)	122 (25)	<0.0001
DBP, mmHg (SD)	80 (16)	77 (15)	0.0063	78 (14)	74 (13)	<0.0001
LVEF, %, median (IQR)	59 (54–66)	59 (54–65)	0.53	32 (24–39)	30 (23–38)	0.0006

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; HF-PEF, heart failure with preserved ejection fraction; HF-REF, heart failure with reduced ejection fraction; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

higher in-hospital and early post-discharge mortality when compared with patients with higher serum sodium levels. The association between serum sodium concentration and in-hospital mortality was independent of left ventricular systolic function.[2] The Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study[12] had longer follow-up and reported a strong association between low sodium levels and 1-year mortality. Serum sodium levels <138 mmol/L were predictive of 3-year mortality in the Seattle Heart Failure Model, but this study did not include patients with HF-PEF.[11] The present analysis of the MAGGIC data set confirms previous findings and demonstrates that in a wide range of patients with reduced and with preserved LVEF, low serum sodium is strongly associated with all-cause mortality over a 3-year follow-up. The powerful prognostic impact of hyponatraemia was still observed after adjustment for other variables of clinical relevance in HF such as age, gender, diabetes, ischaemic heart disease, and renal function.

Serum sodium is a modifiable parameter, and changes in serum sodium concentration seem to influence outcome in patients with HF.[4,26,27] A recent study suggests that patients with decompensated HF who exhibit an increase in serum sodium after hospital discharge have improved survival compared with patients in whom serum sodium remains unchanged or decreases.[27] It is, however, still unclear what represents a clinically meaningful change (increase or decrease) in serum sodium concentration in HF patients and what is the most appropriate cut-off level of serum sodium that should be used to define hyponatraemia.[2,28] In the OPTIMIZE-HF registry, a 'U'-shaped relationship was found between serum sodium concentration and in-hospital mortality, with mortality already starting to increase for sodium levels between 135 and 138 mmol/L compared with levels >138 mmol/L.[2] A post-hoc analysis from the International Collaborative of NT-proBNP (ICON) showed a similar shape for the association between serum sodium concentration and 1-year mortality in acute HF patients.[13] In contrast to these findings, we observed a linear increase in the risk of 3-year all-cause mortality at values <140 mmol/L, and a plateau at sodium levels ≥ 140 mmol/L. This suggests that in patients with HF, mortality may increase within the standard reference limits of serum sodium (135–140 mmol/L) compared with ≥140 mmol/L. However, we cannot establish an optimal prognostic threshold because prediction intervals were relatively wide. Further therapeutic studies need to take into consideration these issues and target exclusively patients with hyponatraemia.

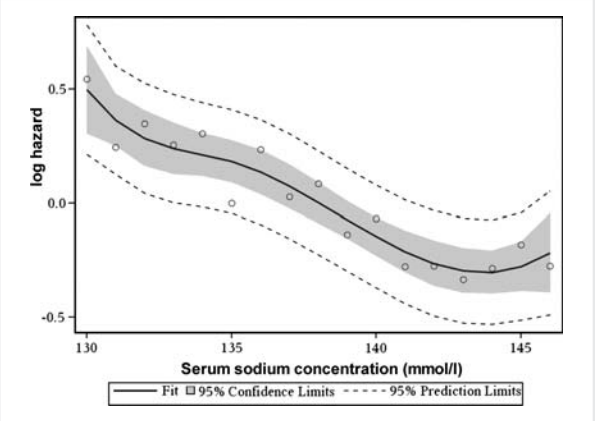

Figure 2 Association between serum sodium concentration and the risk of death from any cause at 3 years. Hazard ratio (solid line) and 95% confidence intervals are estimated in a Cox proportional hazards model using spline piecewise polynomials with one knot at 135 mmol/L. The model is adjusted for age, gender, ejection fraction group, hypertension, ischaemic aetiology, diabetes mellitus, and atrial fibrillation, and stratified by study.

Table 3 Relative risk of all-cause death associated with hyponatraemia (serum sodium concentration <135 mmol/L)

	n	All-cause death, HR (95% CI)
Overall		
Model 1	14 766	1.64 (1.48–1.81)
Model 2[a]	14 766	1.64 (1.47–1.82)
Model 3[a]	11 954	1.60 (1.43–1.78)
Heart failure with reduced ejection fraction		
Model 1	11 029	1.72 (1.53–1.93)
Model 2	11 029	1.69 (1.50–1.91)
Model 3	8803	1.64 (1.45–1.86)
Heart failure with preserved ejection fraction		
Model 1	3737	1.36 (1.08–1.72)
Model 2	3737	1.40 (1.10–1.79)
Model 3	2988	1.35 (1.06–1.72)

Model 1: adjusted for age and gender.
Model 2: adjusted for age, gender, ischaemic aetiology, hypertension, diabetes mellitus, atrial fibrillation, and stratified by study.
Model 3: adjusted for age, gender, ischaemic aetiology, hypertension, diabetes mellitus, atrial fibrillation, estimated glomerular filtration rate, and stratified by study.
CI, confidence interval; HR, hazard ratio.
[a]Models 2 and 3 in the overall cohort were also adjusted for left ventricular ejection fraction (<50% and ≥50%).

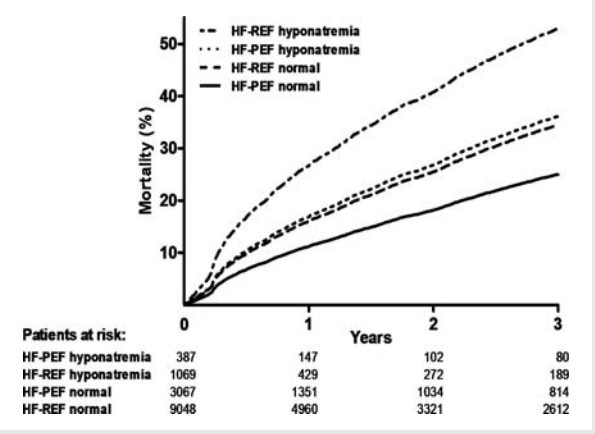

Figure 3 Mortality for patients with HF-REF (heart failure with reduced ejection fraction) and for patients with HF-PEF (heart failure with preserved ejection fraction) according to the presence or absence of hyponatraemia. Adjusted for age, gender, aetiology, hypertension, diabetes, and atrial fibrillation.

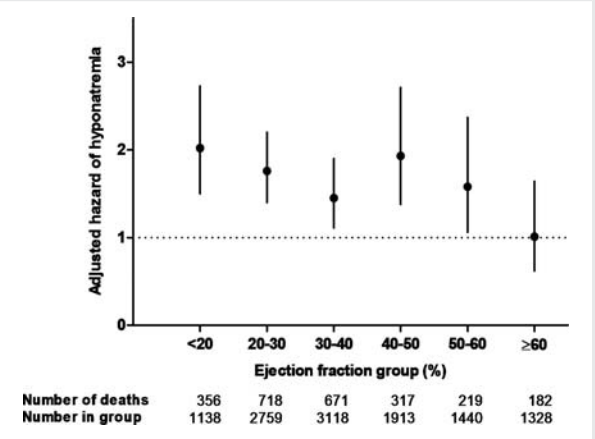

Figure 4 Adjusted hazard ratios comparing death from any cause associated with hyponatraemia by groups of left ventricular ejection fraction.

Given the pathogenic role of AVP activation in HF, the therapeutic targeting of AVP action seems a logical approach. Several AVP antagonists are available and have been tested in clinical trials. Tolvaptan is a V_2 receptor antagonist approved for the treatment of clinically significant hypervolaemic and euvolaemic hyponatraemia (serum sodium <125 mmol/L) in patients with cirrhosis, HF, or syndrome of inappropriate antidiuretic hormone. The SALT trials showed that tolvaptan increases serum sodium and improves hyponatraemia-related symptoms and quality of life in cases of hypervolaemic or euvolaemic hyponatraemia.[29] Although effective in reducing body weight, increasing urine output, and reducing congestive symptoms, tolvaptan did not reduce all-cause mortality, cardiovascular mortality, and HF hospitalizations in the large Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial.[17] Interestingly, patients included in EVEREST had extremely high angiotensin-converting enzyme inhibitor and beta-blocker prescription rates and only 8% had hyponatraemia (serum

sodium <134 mmol/L). Our analysis suggests that the cut-off for the serum sodium level is crucial when looking at mortality in patients with HF-REF and patients with HF-PEF and in designing future trials of AVP antagonists in HF.

Limitations

The current study has some limitations. While the MAGGIC meta-analysis has combined the data from a large number of studies and individual patients, our analysis is limited by the underlying limitations of the original individual studies. However, by incorporating data from both randomized trials and observational studies, resulting in a wide range of patients, with long follow-up and a large number of clinical events, the results are likely to be an accurate reflection of patients with HF seen in routine clinical practice. Data on clinical, echocardiographic, and laboratory variables were not universally available in all studies. The MAGGIC meta-analysis has included a large number of studies, and to derive a common data set we were able to collect key covariates. This provides great statistical power for determining the role of major variables in relation to outcome. However, the limitation of such meta-analyses is that data on other variables of potential relevance are not available in sufficient numbers to be included in the multivariable models. This is an inherent limitation but does not preclude using the available data to address important clinical hypotheses. Cause-specific mortality was not available in all studies, and therefore we took into consideration only all-cause mortality. Finally, data were incorporated only from studies that enrolled patients without an LVEF inclusion criterion at baseline. Therefore, studies such as I-PRESERVE and PEP-CHF and the numerous individual studies of patients with HF-REF were not included in this meta-analysis.

Conclusion

The analysis of this large data set combining individual patients from multiple studies shows that a low serum sodium concentration is a strong determinant of long-term mortality in a wide spectrum of patients with HF, irrespective of LVEF. The excess risk associated with low serum sodium concentration becomes obvious below 140 mmol/L. Whether targeting hyponatraemia based on this cut-off level translates into clinical benefit remains to be established by future research.

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Conflict of interest: M.K. is a member of the Executive Committee of the I-PRESERVE trial and is an officer of the European Society of Cardiology. M.W.R. has received research funding from Astellas Pharma US (small grant) and Sanofi-Aventis (consultant, moderate). The remaining authors have no conflicts of interest.

Appendix

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