Original Article

The prognostic significance of serum sodium in a population undergoing cardiac resynchronisation therapy

Kaushik Guha[a,b,*], Jens Spießhöfer[a,b,c], Adam Hartley[d], Simon Pearse[a,b], Philip Y. Xiu[a,b], Rakesh Sharma[a,b]

[a] Dept of Cardiology, Royal Brompton Hospital, London, United Kingdom
[b] National Heart and Lung Institute, Imperial College London, London, United Kingdom
[c] Dept of Respiratory Medicine, Hannover Medical School, Hannover, Germany
[d] Dept of Cardiology, Harefield Hospital, London, United Kingdom

ARTICLE INFO

ABSTRACT

Purpose: To determine the prognostic implications of changes towards hyponatremia at varying time-points in the treatment of patients undergoing cardiac resynchronisation therapy (CRT).
Methods: A retrospective series of 249 patients was studied from 2002 to 2013. The population was categorized on the basis of serum sodium profile at baseline, at 1 month and at 6 month follow up visits following successful CRT implantation. The composite endpoint was all-cause mortality and heart failure hospitalisation (defined by the need for intravenous diuretic therapy) following CRT implantation.
Results: A total of 249 patients (67.8 ± 12.5 years; NYHA class III/IV 75; LVEF 27.2 ± 8.8%) were followed up for a median of 5.5 years. Hyponatremia at baseline, 1 month or 6 months follow up did not predict the composite endpoint. 26% of patients showed hyponatremia at baseline prior to CRT implantation, while it was present in 19.9% of patients 1 month ($p = 0.003$) and in 16% ($p < 0.001$) 6 months after CRT implantation. There was a significantly worse outcome for those patients who developed hyponatremia 6 months after CRT implantation. In multivariate analysis, the intake of loop diuretics (HR 1.76 [1.04–2.95], $p = 0.03$) and renal impairment (urea > 7.0 mmol/l) (HR 1.61 [1.05–2.46], $p = 0.03$) at baseline were associated with an increased risk of unplanned heart failure hospitalisation and all-cause mortality after CRT implantation.
Conclusions: A change towards hyponatremia when observed 6 months after CRT implantation may predict a worse clinical outcome. Additionally, renal impairment and higher diuretic doses are associated with an increased risk of mortality in the population analysed.
© 2017 Published by Elsevier B.V. on behalf of Cardiological Society of India. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Hyponatremia (defined as serum sodium <135 mmol/l) has previously been described to be an adverse prognosticator in populations with heart failure.[1–3] Hyponatremia and changes towards hyponatremia have been suggested to be associated with adverse outcomes in patients undergoing CRT implantation.[4,5]

This study aimed to determine whether hyponatremia is an adverse prognosticator in patients undergoing CRT implantation by investigating (1) whether the time-point of the hyponatremia influences its prognostic value (i.e. before CRT implantation, 1 month and 6 months after); (2) examining whether change in serum sodium may have independent prognostic significance and (3) whether further prognosticators of adverse outcomes after CRT implantation could be identified.

2. Methods

A series of 285 patients undergoing CRT implantation from a single tertiary university centre was studied. The trial period was between 2002 and 2013.
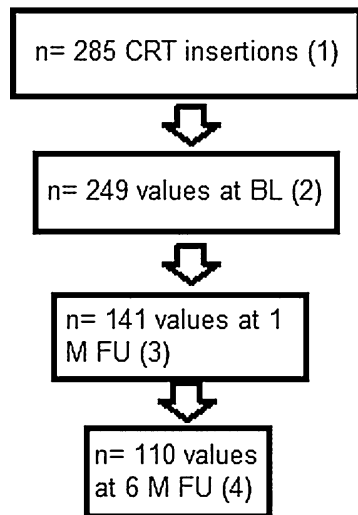
Fig. 1. Flow chart of patients being inserted a CRT device (1), with available data on sodium at baseline (2), at a 1 month follow up visit (3), at a 6 months follow up visit (4).

All implants were performed as per contemporary guidelines.[7–9] Prior to implantation clinical, biochemical and cardiac imaging data was recorded. This included NYHA status, documenting clinical variables including systolic blood pressure and using transthoracic echocardiography to derive a Biplane Simpson's measure of left ventricular ejection fraction, a measure of the 12 lead electrocardiogram QRS duration was also documented.

The patient then received CRT as per the contemporary guidance and had CRT implanted via standard transvenous techniques. A conventional range of generators and leads was used. All individuals were then systematically reviewed in the dedicated heart failure pacing clinic at 1 month whereby the serum sodium was again measured and within the heart failure service at 6 months. Baseline measurement was up to 48 h prior to CRT implantation.

Hyponatremia was defined as per the current guidance from the European Society of Cardiology-2012 as a serum sodium level <135 mmol/l.[9]

The endpoint was defined as a composite of emergency unplanned hospitalisation for heart failure which required the use of intravenous diuretics and all-cause mortality. The analysis was time to first event driven.

Statistical analyses were performed using Sigma Plot software (Version 11.0, Systat Software Ltd.), while Kaplan Meier Curves were created using GraphPad Prism (Version 5.00 GraphPad Software).

Data are depicted as mean value $\pm$ standard deviation (SD) for continuous variables, for which differences between groups were compared by a t-test. A paired t-test was used to detect changes in individual patients with time. The Mann–Whitney Rank Sum test was used for non-normally distributed data. Categorical data are summarized as frequencies and percentages and the Chi-square test was used to compare differences between groups.

Kaplan–Meier curves were constructed to compare event rates in hyponatremic and normonatremic groups with respect to the composite end point after CRT insertion.

This was done separately for those patients with available sodium values at baseline, at 1 month and at 6 months follows up and for different patient groups based on their changes in sodium from baseline to 1 month follow up and from baseline to 6 months follow up.

The difference between survival curves was assessed by the log-rank (Mantel–Cox) test.

To assess baseline predictors of the composite endpoint, univariate Cox proportional hazards were calculated, which required a categorisation of continuous variables if they failed to

Table 1
Baseline characteristics (frequency or mean $\pm$ standard deviation) for the entire cohort and hyponatremic and normonatremic patients.

Characteristic	Whole cohort $n = 249$	Hyponatremia $n = 50$	Normonatremia $n = 199$	p-Value
Age (years)	67.8 ± 12.6	66.7 ± 11.9	68.1 ± 12.7	0.444
Female	54 (21%)	12 (24%)	42 (21%)	0.173
Creatinine (μmol/l)	120 ± 53	121 ± 56	121 ± 52	0.899
Urea (mmol/l)	10 ± 6	11 ± 6	10 ± 6	0.221
Sodium at baseline (mmol/l)	137 ± 3	132 ± 2	138 ± 2	<0.001
Hemoglobin (mg/dl)	13.0 ± 1.6	12.9 ± 1.6	13.1 ± 1.6	0.450
Systolic BP (mmHg)	116.8 ± 21.2	112.1 ± 23.4	118.0 ± 20.5	0.021
Diastolic BP (mmHg)	69.7 ± 13.8	69.1 ± 12.8	69.9 ± 14.1	0.549
NYHA class III/IV (%)	187 (75%)	42 (84%)	145 (73%)	0.407
LVEF (%) [missing]	27.2 ± 8.7 [46]	25.3 ± 8.7 [10]	27.6 ± 8.6 [36]	0.130
LVIDd (mm) [missing]	6.6 ± 1.0 [46]	6.7 ± 1.0 [10]	6.6 ± 1.0 [36]	0.408
LVIDs (mm) [missing]	5.6 ± 1.1 [46]	5.6 ± 1.1 [10]	5.6 ± 1.1 [36]	0.800
QRS duration (ms)	161.4 ± 28.2	165.6 ± 33.3	160.3 ± 26.8	0.195
Ischaemic HF	125 (50%)	18 (36%)	107 (54%)	0.399
Non Ischeamic HF	124 (50%)	32 (64%)	92 (46%)	0.399
Atrial fibrillation	57 (23%)	9 (18%)	48 (24%)	0.214
Diabetes mellitus	58 (23%)	12 (24%)	46 (23%)	0.304
Hypertension	62 (25%)	12 (24%)	50 (25%)	0.686
Medications				
Angiotensin converting enzyme inhibitor	157 (63%)	34 (68%)	123 (62%)	0.514
Angiotensin receptor blocker	67 (27%)	12 (24%)	55 (28%)	0.379
Aldosterone antagonist	(54%)	(66%)	(51%)	0.232
Total daily dose of aldosterone antagonist	13.7 ± 13.4	16.8 ± 13.5	12.8 ± 13.3	0.071
Beta-blockers	165 (66%)	30 (60%)	135 (68%)	0.479
Digoxin	45 (18%)	10 (20%)	35 (18%)	1.000
Diuretics	203 (82%)	44 (88%)	159 (80%)	1.000
Total daily dose of Lasix[a] (mg)	53.4 ± 49.2	60.0 ± 51.0	51.7 ± 48.8	0.246

Hypertension = blood pressure $\geq 140/90$ mmHg.
[a] Total daily dose of Lasix or Lasix equivalent (1 mg bumetanide = 40 mg frusemide).

show a normal distribution. A stepwise multivariate model was used to assess variables shown to be independently associated with the outcome in the univariate model.

For this analysis, variables that were significant at $p < 0.15$ were included in the model. For these analyses, the proportional hazard assumptions were tested. Sample size calculation was not performed.

3. Results

Of 285 patients in our database, there was baseline data in 249 patients with regards to sodium levels. 1 month following CRT implantation, 141 patients had a documented sodium concentration and at 6 months 110 patients had serum sodium measured.

Fig. 1 depicts the patient flow diagram for the study. Table 1 describes baseline characteristics of the enrolled patients.

In our cohort of 249 patients the mean age was 67.8 ± 12.6 years with a mean LVEF before CRT implantation of $27.2 \pm 8.7\%$ and a mean QRS width before CRT implantation of 161.4 ± 28.2 ms. 50% of patients presented with an ischaemic cause of their HF.

Patients with hyponatremia at baseline had a significantly lower systolic blood pressure compared to normonatremic patients (112.1 ± 23.4 vs. 118.0 ± 20.5 mmHg; $p = 0.021$). In addition, hyponatremic patients tended to have a higher total daily dose of mineralocorticoid receptor antagonists (MRA) (16.8 ± 13.5 vs. 12.8 ± 13.3 mg; $p = 0.071$). Other than these two factors, the baseline characteristics of the two groups of patients did not differ significantly.

Overall, the median follow up period for the 249 patients enrolled in our study was 2141 days (IQR 1293 days). A total of 139 events (hospitalisation or all-cause mortality, whichever occurred first) were recorded, with 54 events being hospitalisations and 85 being all-cause mortality.

Of 199 patients presenting with normonatremia at baseline 108 patients (54%) reached the composite endpoint (42 hospitalisations and 66 deaths), while in 50 patients presenting with hyponatremia at baseline 31 events (62%) were recorded (12 hospitalisations and 29 deaths).

No statistically significant difference in event-free survival was found between the 50 patients presenting with hyponatremia at baseline (31 reached the endpoint) compared to the 199 patients presenting with normonatremia (108 reached the endpoint, log rank test $p = 0.49$; Fig. 1).

Equally, no statistically significant difference in event free survival was found between the 28 patients presenting with hyponatremia at 1 month follow up (19 reached the endpoint) compared to those 113 presenting with normonatremia (58 reached the endpoint, log rank test $p = 0.18$; Fig. 2).

The same applies to hyponatremia at 6 months follow up. No statistically significant difference in event free survival was found between those 17 patients presenting with hyponatremia at a 6 month follow up visit (13 reached the endpoint) compared to those 93 (56 reached the endpoint) patients presenting with normonatremia (log rank test $p = 0.12$; Figs. 3 and 4). There was no significance when HF hospitalisation and all-cause mortality were analysed separately as respective endpoints.

Table 2 presents the univariate Cox analysis of the hazard ratios of different variables in predicting the occurrence of the composite end point.

In this model and consistent with the Kaplan Meier curves, hyponatremia at baseline, at 1 month and at 6 months follow up was not predictive of the composite endpoint.

However, age (HR 1.030; 95% CI 1.014–1.050; $p < 0.001$), impaired renal function defined as creatinine > 110 μmol/l (HR 1.789; 95% CI 1.264–2.533; $p = 0.001$) and urea > 7.0 mmol/l (HR 2.084; 95% CI 1.390–3.125; $p < 0.001$), ischaemic aetiology (HR

Fig. 2. Kaplan Meier curve comparing event free survival in patients after CRT insertion between patients with normonatremia and hyponatremia at baseline.

1.574; 95% CI 1.124–2.203; $p = 0.008$), use of aldosterone antagonists (HR 1.505; 95% CI 1.065–2.126; $p = 0.020$) and loop diuretics (HR 2.152; 95% CI 1.295–3.575; $p = 0.003$) were associated with an increased risk of reaching the composite end point.

In a stepwise multivariate model, age (HR 1.021; 1.004–1.038; $p = 0.018$), urea > 7.0 mmol/l (HR 1.607; 1.049–2.461; $p = 0.029$) and

Fig. 3. Kaplan Meier curve comparing event free survival in patients after CRT insertion between patients with normonatremia and hyponatremia at 1 month follow up.

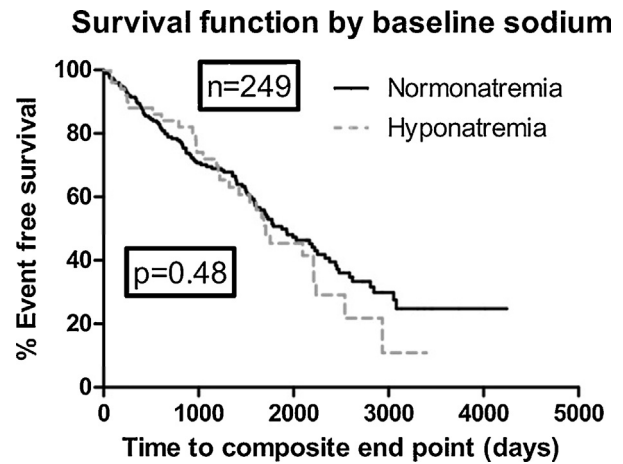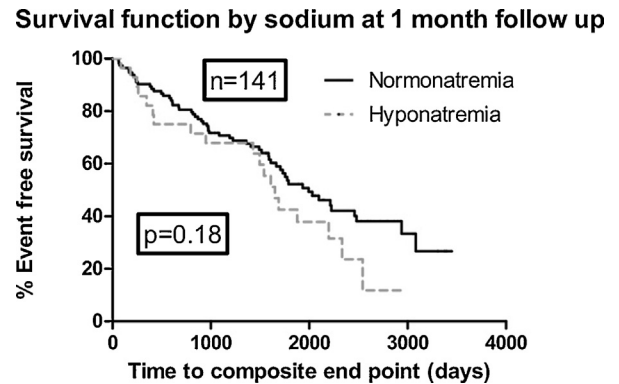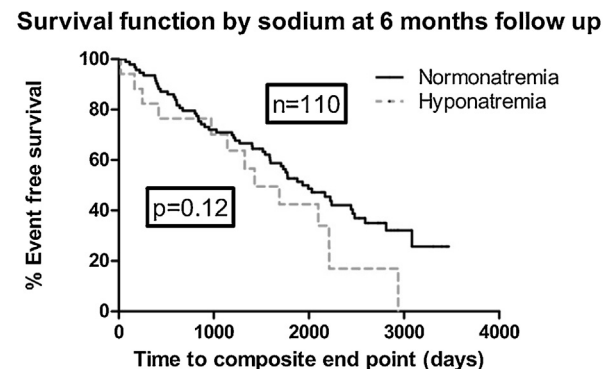**Fig. 4.** Kaplan Meier curve comparing event free survival in patients after CRT insertion between patients with normonatremia and hyponatremia at 6 months follow up.

Table 2
Univariate and multivariate Cox regression models to identify predictors for composite end point.

Characteristic	Univariate		Multivariate	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age	1.030 (1.014–1.050)	<0.001	1.021 (1.004–1.038)	0.018
Creatinine (>110 μmol/l)	1.789 (1.264 –2.533)	0.001		
NYHA class III/IV	1.295 (0.875–1.915)	0.197		
Urea (>7.0 mmol/l)	2.084 (1.390–3.125)	<0.001	1.607 (1.049–2.461)	0.029
Hyponatremia at baseline	1.155 (0.774–1.724)	0.481		
Hyponatremia at 1 MFU	1.325 (0.788–2.229)	0.289		
Hyponatremia at 6 MFU	1.179 (0.644–2.156)	0.594		
Hemoglobin	0.928 (0.835–1.032)	0.169		
Systolic BP	0.998 (0.991–1.006)	0.611		
Diastolic BP	0.992 (0.980–1.003)	0.165		
LVEF (%)	0.995 (0.974–1.016)	0.610		
LVIDd	1.016 (0.849–1.216)	0.861		
LVIDs	1.012 (0.859–1.193)	0.885		
QRS duration	1.001 (0.995–1.008)	0.678		
Ischaemic HF	1.574(1.124–2.203)	0.008	1.304 (0.916–1.857)	0.141
Atrial fibrillation	1.383 (0.943–2.030)	0.097		
Diabetes mellitus	1.429 (0.969–2.108)	0.072		
Hypertension	0.946 (0.634–1.412)	0.787		
Aldosterone antagonist	1.505 (1.065–2.126)	0.020		
Loop diuretics	2.152 (1.295–3.575)	0.003	1.755 (1.042–2.954)	0.034
Thiazide diuretics	1.317 (0.728–2.381)	0.363		

the intake of loop diuretics (HR 1.755; 1.042–2.954; $p = 0.034$) continued to remain significantly associated with the composite end point.

37/141 (26%) patients were hyponatremic at baseline and 28/141 (20%) at a 1 month follow up visit ($p = 0.003$), while 28/110 (26%) patients were hyponatremic at baseline and 17/110 (16%) patients were hyponatremic at a 6 months follow up visit ($p < 0.001$). Fig. 5 shows that there was no statistically significant difference in survival when dividing patients into four groups based on their changes in hypo/normonatremia from baseline to 1 month. In contrast Fig. 6 shows a statistically significant difference when comparing changes in hyponatremia/normonatremia from baseline to 6 months follow up. Especially those patients becoming hyponatremic 6 months after CRT implantation show the worst outcome when compared to all other groups of patients.

4. Discussion

The main finding from this study was that neither baseline hyponatremia nor hyponatremia at 1 or 6 months following CRT implantation was associated with adverse outcomes. Notably several patients experienced a change in serum sodium status with some becoming hyponatremic at 6 months following CRT implantation which did predict a worse clinical outcome. Additionally, renal impairment and higher diuretic doses are associated with an increased risk of mortality.

The prevalence of hyponatremia in HF patients has been suggested to be about 20% in patients in prior registry data.[2] Hence the prevalence of hyponatremia of 20% within the cohort is consistent with previous observations.

However, the causes of hyponatremia in heart failure are complex and multifactorial.[1,2,10] HF precipitates a neurohormonal response, including activation of renin–angiotensin–aldosterone system (RAAS), arginine vasopressin release, and up-regulation of sympathetic nervous activity.[1,10] This has the net result of reducing renal water excretion and leads to a dilutional hyponatremia.[1,10]

In addition, sodium excretion from the kidney is enhanced by the action of diuretics and the presence of renal dysfunction.[10–12] ACE inhibitors and aldosterone antagonists as prognostically
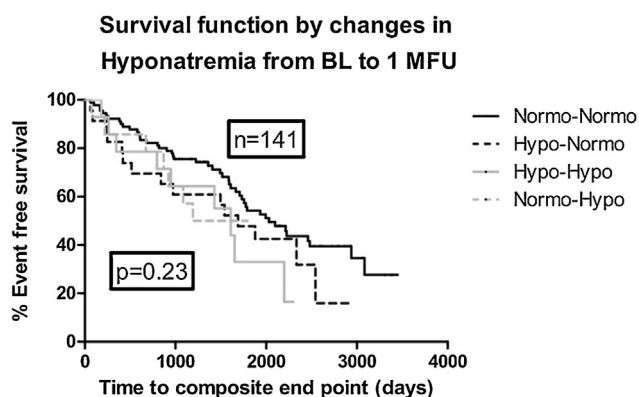
Fig. 5. Kaplan Meier curve comparing event free survival in patients after CRT insertion between different patient groups: (1) normonatremic patients who stay normonatremic 1 month after CRT device implantation; (2) hyponatremic patients who become normonatremic 1 month after CRT device implantation; (3) hyponatremic patients who stay hyponatremic 1 month after device implantation; and (4) normonatremic patients who become hyponatremic 1 month after device implantation.
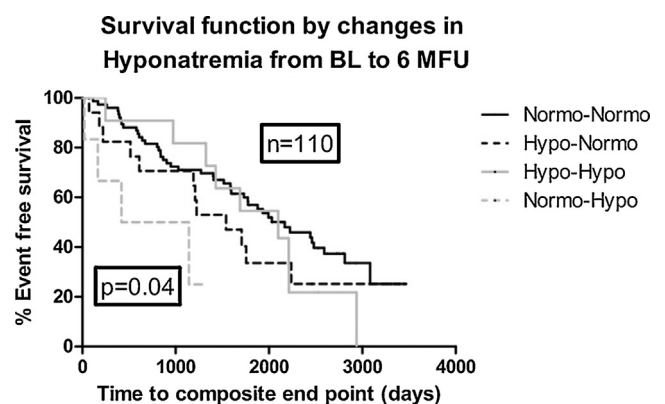
Fig. 6. Kaplan Meier curve comparing event free survival in patients after CRT insertion between different patient groups: (1) normonatremic patients who stay normonatremic 6 months after CRT device implantation; (2) hyponatremic patients who become normonatremic 6 months after CRT device implantation; (3) hyponatremic patients who stay hyponatremic 6 months after device implantation; and (4) normonatremic patients who become hyponatremic 6 months after device implantation.

beneficial neurohormonal inhibitors as well as diuretics, further modulate sodium and water balance in HF.[10,12]

Beyond this, serum sodium within heart failure patients may also correlate with central venous pressure. Central venous pressure has been shown to correlate with levels of right ventricular dysfunction which have also been shown to be adverse prognosticators in heart failure patients.[11,13,14] In sum, hyponatremia might reflect the severity of HF and has therefore been identified as a bad prognosticator in patients with HF. However, as described, serum sodium is not a reflection of any one process and is likely to be a complex marker of the multiple aberrant homeostatic and therapeutic pathways encountered within a patient with left ventricular systolic dysfunction (LVSD).[10,15,16]

Cardiac resynchronisation therapy has been demonstrated to be effective at reducing morbidity and mortality in patients with symptomatic left ventricular dysfunction on optimal tolerated medical therapy with a broadened QRS duration. Therefore, hyponatremia as a mirror of an impaired cardiac function was shown to resolve in patient populations undergoing CRT implantation. Despite the positive results from clinical trials, there are a significant number of patients who fail to gain benefit and there is a high need for simple variables that help predict what patients will gain benefit from CRT implantation. The reasons for a lack of clinical response from CRT are multifactorial, including renal impairment and right ventricular dysfunction.[6,9,17]

However it has also been previously observed that CRT may take up to three-six months to induce positive LV remodelling, symptomatic improvement and B type natriuretic peptide reduction.[18] Due to the complexity of this effect an absolute value during this period of time may represent the changing physiology. Therefore an absolute value of serum sodium is unlikely to predict clinical outcomes, which is what has been observed within this dataset.

However due to the complex changes in physiology which may also be exploited by adjusting prognostically beneficial heart failure medication, within our data the patients who became hyponatremic by the end of 6 months did have reduced survival and increased hospitalisation.[19] This may reflect a failure to undergo left ventricular remodelling or have other beneficial responses due to advanced biventricular disease 6 months after implantation and may have a predictive value in clinical practice.

In our dataset renal impairment and higher diuretic doses at baseline were shown to be associated with an increased risk of mortality even after CRT implantation. As found in the study of Levy et al., renal impairment and daily intake of diuretics were associated with a worse outcome.[20] This may be expected as the need for high diuretic doses is associated with more advanced cardiorenal dysfunction.[12] This may be considered when evaluating potential benefit from CRT.

Two previous studies have analysed the relationship between hyponatremia and clinical outcomes in populations undergoing CRT implantation.[4,5]

Sharma and co-authors describe a retrospective series of 402 patients who were analysed for the relationship between serum sodium and a composite outcome of all-cause mortality, hospitalisation for HF, implantation of a left ventricular assist device and cardiac transplantation.[5] In accordance with our data the group established that a change towards hyponatremia within 3–6 months after CRT implantation is associated with a poorer clinical outcome. Also in accordance with our findings an impaired renal function and the intake of diuretics at baseline predicted a worse clinical outcome. However, in contrast to our results hyponatremia at baseline has been found to predict response to CRT as defined by an increase in LVEF and to predict clinical outcome.

The baseline data however demonstrates significant differences within the populations with hyponatremia and normotremia with medication and diabetes mellitus. There is no further control applied to the group for further statistical analysis. Hence by significant con founders being present the overall conclusions presented may be debatable. All of the significant confounders both directly or indirectly influence serum sodium and hence impact upon final conclusions. The time period of follow up within this study is 5.5 years however an arbitrary three year follow up period was chosen for the study by Sharma and colleagues. Hence again with a longer period of follow up a different relationship may have been obtained.

Arao and co-authors found impaired renal function and low serum sodium to be independently associated with a worse clinical outcome after CRT insertion.[4] This is a small, underpowered single centre study and there was no attempt to control for confounders in the multivariate model.

Overall, our findings go beyond the previous work showing that CRT can resolve hyponatremia and that hyponatremia 6 months following CRT implantation is a predictor of all-cause mortality and heart failure hospitalisation. The role of a solitary measurement of sodium as a predictor for clinical outcomes after CRT implantations has to be scrutinized. More importantly, patients need meticulous follow up and relative changes in sodium might amongst other factors predict clinical outcomes in patients after a CRT implantation.

Those conclusions are drawn based on a well selected cohort of HF patients with a median follow up of >5.5 years and consideration of numerous potential confounding factors.

4.1. Limitations

Firstly, this study analysed a retrospective data series from a large university teaching hospital. Therefore it is subject to the usual limitations of missing data, limited follow up and non-uniform follow up. Hence the dataset should be viewed accordingly and conclusions derived viewed with caution. The clinical service is a tertiary/quaternary heart failure service with all patients having been proposed for CRT by a cardiologist with expertise in heart failure. All follow up was then within the same heart failure service and hence where necessary prognostically beneficial heart failure medication was up titrated following successful CRT implantation. Hence again the results from this study may not be readily applicable to other datasets and populations.

Secondly, frequent changes in drug prescription and compliance over time are likely to affect sodium balance, which was not possible to correct for in our research or that of others. Cardiac output and blood pressure usually rise in responders after CRT allowing up-titration of HF medication and consequent alteration of sodium balance.[19]

Thirdly, as we did not record LVEF at follow up, we cannot determine whether changes in serum sodium mirrored changes in EF, known to be linked to prognosis with CRT therapy.

5. Conclusion

Absolute baseline hyponatremia does not predict clinical outcomes in patients undergoing CRT implantation. Nor do values at 1 or 6 months. However those patients who become hyponatremic at 6 months following CRT implantation are associated with clinically adverse outcomes. The relationship needs further investigative work.

Conflicts of interest

The authors have none to declare.

References

1. Goldsmith SR. Treatment options for hyponatremia in heart failure. *Heart Fail Rev*. 2009;14:65–73.
2. Gheorghiade M, Abraham WT, Albert NM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J*. 2007;28:980–988.
3. Tepper D, Harris S, Ip R. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE trial. *Congest Heart Fail*. 2008;14:46.
4. Arao K, Fujiwara T, Sakakura K, et al. Hyponatremia as a predictor for worsening heart failure in patients receiving cardiac resynchronization therapy. *Circ J*. 2012;77:116–122.
5. Sharma AK, Vegh EM, Kandala J, et al. Usefulness of hyponatremia as a predictor for adverse events in patients with heart failure receiving cardiac resynchronization therapy. *Am J Cardiol*. 2014;114:83–87.
6. Dickstein K, Vardas PE, Auricchio A, et al. Focused Update of ESC Guidelines on device therapy in heart failure. *Eur Heart J*. 2010;31:2677–2687.
7. Vardas PE, Auricchio A, Blanc J-J, et al. Guidelines for cardiac pacing and cardiac resynchronization therapy: The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Eur Heart J*. 2007;28:2256–2295.
8. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur Heart J*. 2008;29:2388–2442.
9. Mcmurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur J Heart Fail*. 2012;14:803–869.
10. Sica D. Hyponatremia and heart failure – treatment considerations. *Congest Heart Fail*. 2006;12:55–60.
11. Cowie MR. Does renal impairment increase mortality risk in patients with heart failure? *Nat Clin Pract Cardiovasc Med*. 2007;4:20–21.
12. Guazzi M, Gatto P, Giusti G, et al. Pathophysiology of cardiorenal syndrome in decompensated heart failure: role of lung–right heart–kidney interaction. *Int J Cardiol*. 2013;169:379–384.
13. Mentz RJ, Kelly JP, von Lueder TG, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol*. 2014;64:2281–2293.
14. Damman K, van Deursen VM, Navis G, et al. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol*. 2009;53:582–588.
15. Lien Y-HH, Shapiro JI. Hyponatremia: clinical diagnosis and management. *Am J Med*. 2007;120:653–658.
16. Oren RM. Hyponatremia in congestive heart failure. *Am J Cardiol*. 2005;95:2B–7B.
17. Cleland JGF, Calvert MJ, Verboven Y, et al. Effects of cardiac resynchronization therapy on long-term quality of life: An analysis from the Cardiac Resynchronisation-Heart Failure (CARE-HF) study. *Am Heart J*. 2009;157:457–466.
18. Gold MR, Daubert C, Abraham WT, et al. The effect of reverse remodeling on long-term survival in mildly symptomatic patients with heart failure receiving cardiac resynchronization therapy: results of the REVERSE study. *Heart Rhythm*. 2015;12:524–530.
19. Kachboura S, Ben Halima A, Ibn Elhadj Z, et al. Cardiac resynchronization therapy allows the optimization of medical treatment in heart failure patients. *Ann Cardiol Angeiol*. 2013;63:17–22.
20. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*. 2006;113:1424–1433.