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ORIGINAL ARTICLE

Parameters of Mineral Metabolism predict Midterm Clinical Outcome in End-Stage Heart Failure Patients

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Abstract

Objectives. We investigated to which extent disturbances in mineral metabolism predict 90-day clinical outcome in end-stage heart failure patients. *Design*. Among numerous biochemical parameters, we measured serum levels of sodium and magnesium, the calciotropic hormones parathyroid hormone and 1,25-dihydroxyvitamin D as well as fibroblast growth factor-23 (a phosphaturic hormone) in 305 cardiac transplant candidates. Primary endpoint was a composite of the need of mechanical circulatory support (MCS), transplantation, or death. *Results.* Of the study cohort, 33.4% reached the primary endpoint. In detail, 19% were transplanted (the vast majority was listed 'high urgent'), 8.8% died and 5.6% received MCS implants. As determined by logistic regression analysis, all aforementioned biochemical parameters were independently related to the primary endpoint. Results did not change substantially when transplanted patients were censored. A risk score (0–5 points) was developed. Of the patients who scored 5 points 89.5% reached the primary endpoint whereas of the patients with a zero score only 3.8% reached the primary endpoint. *Conclusions.* Our data demonstrate that in addition to the well-known predictive value of disturbed sodium metabolism, derangements in calcium, phosphate, and magnesium metabolism also predict midterm clinical outcome in end-stage heart failure patients.

Key words: *survival, mortality, mechanical circulatory support, fibroblast growth factor-23, 1,25-dihydroxyvitamin D, cardiac transplantation*

Introduction

The clinical prognosis of congestive heart failure (CHF) is still unsatisfying. End-stage CHF patients have high annual mortality rates of up to 50% (1,2). Mechanical circulatory support (MCS) implants can significantly prolong survival in end-stage CHF patients (2,3), whereas cardiac transplantation (CTx) is the last option for treating therapy-resistant end-stage CHF (4,5).

Factors influencing the prognosis of end-stage CHF patients are poorly understood. There is some evidence that derangements in the metabolism of specific minerals are of clinical importance. The presence of hyponatremia, for example, correlates with both the severity of CHF and its ultimate outcome (6). In addition, hypomagnesemia is common in CHF patients with NYHA functional class III/IV (7). Derangements in calcium (Ca) and phosphate (PO_4) metabolism are also frequent in CHF and are associated with low circulating concentrations of the calciotropic hormones 25-hydroxyvitamin D (25[OH] D) and 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) (8,9). Both, low 25(OH)D and low $1,25(OH)_2D$ concentrations are associated with poor prognosis in CHF (10,11). Fibroblast-growth factor (FGF)-23 is a newly recognized phosphaturic hormone (12) that is associated with increased left ventricular mass (13) and high mortality rates (14).

We sought to investigate in a pilot study to which extent disturbances in biochemical parameters of mineral metabolism predict clinical outcome in end-stage heart failure patients.

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Materials and Methods

Patients and study procedures

Between 2004 and 2006, we collected blood samples from 305 patients on the Eurotransplant List awaiting cardiac transplantation at our institution. Patients with cardiac re-transplantation and/or with an age of less than 18 years were excluded. Further, we excluded 54 patients who were on MCS support. Blood specimens were drawn between 7:00am and 9:00am after a period of 10 to 12 h overnight fasting. Samples were taken during regular outpatient visits (n = 259) or within the first 3 days of hospital admission (n = 46) and immediately centrifuged at 1500g. Aliquots were then frozen at −80 °C for further analysis. In serum/plasma samples, we measured parameters of mineral metabolism such as sodium (Na), PO_4, Ca, magnesium (Mg), vitamin D metabolites, parathyroid hormone (PTH), FGF-23, N-terminal propeptide of brain natriuretic peptide (NTproBNP), parameters of systemic inflammation such as C-reactive protein (CRP) and tumor necrosis factor (TNF)-α, and parameters of myocardial extracellular matrix turnover such as matrix metalloproteinase (MMP)-9 and its tissue inhibitor (TIMP-1). The following auto analysers and bioassays were used: Architect (Abbott, Wiesbaden, Germany): minerals, CRP; Elecsys1010 (Roche, Mannheim, Germany); NTproBNP; Immulite (DPC, Bad Nauheim, Germany): TNF-α, PTH; Radio Immunoassay (DiaSorin, Stillwater, MN, USA): 25(OH)D); Enzyme-linked immunoassay (Immundiagnostik, Bensheim, Germany): $1,25(OH)_2D$; Enzyme-linked immunoassay (R&D, Minneapolis, MN, USA): MMP-9;TIMP-1; and enzyme-linked immunoassay (Immutopics, San Clemente, CA, USA): FGF-23. In addition, we measured serum creatinine as an indicator for renal function and total bilirubin as an indicator for liver function. Glomerular filtration rate (GFR) was estimated by the MDRD formula (15).

Through the patients' electronic records we assessed age, anthropometric data, days spent on the waiting list, diagnoses, concomitant procedures, hemodynamics and echocardiographic parameters. During the study period, neither calcium and vitamin D supplements nor bisphoshonates were routinely given to end-stage heart failure patients at our clinic.

Primary endpoint was a composite of (i) the need of mechanical circulatory support (MCS) such as intra-aortic balloon pump (IABP), extra-corporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or total artificial heart (TAH), (ii) cardiac transplantation, or (iii) any cause of death. Although transplantation may depend on donor availability, this endpoint is primarily an indicator of poor clinical outcome. The Eurotransplant listing system for cardiac transplantation consists of three categories: elective (cardiac index below 2.1 l/min/m^2; ejection fraction below 35%), urgent (hospitalized patients with a cardiac index below 2.1 l/min/m^2 and an ejection fraction below 30%), and high urgent (same criteria as for urgent listing and dobutamine or milrinone requirement). Due to donor shortage, approximately 80% of our patients are listed 'high urgent' before they are transplanted. Consequently, the hemodynamic situation of the majority of patients worsens before transplantation. All patients gave written informed consent for the study procedures. The study was approved by the local Ethics Committee.

Statistics

We report about categorical variables using the percentage of observations. Continuous variables are expressed as mean and standard error of the mean (SEM). We used Fisher's Exact Test, the Mann-Whitney Test and the Kruskal-Wallis Test to compare differences in categorical variables and for continuous variables between the study groups, when appropriate. We performed univariate and multivariate logistic regression analyses to assess biochemical predictors of 90-day event-free survival after blood drawing. Results are presented as hazard ratios (HRs) with a 95% confidence interval (CI). Based on the coefficients of the multivariate analysis a score formula was determined. This formula was used for dividing all patients into the scoring groups. The area under the receiver operation characteristics (ROC) curve was used to assess how clearly the score could discriminate between patients with and without an event. Kaplan-Meier estimates are used to present clinical outcome according to different score groups of deranged mineral metabolism. The log-rank test was used to test for differences between subgroups. A p-value < 0.05 was considered statistically significant. We used the statistical software package PASW, version 18 (Chicago, Illinois, USA), to perform the analyses.

Results

Clinical Outcome of the Study Cohort

During follow up, the primary endpoint was reached by 33.4% of the study cohort. In detail, 17 patients (5.6%) needed MCS support (IABP support, n = 6; ECMO support, n = 1; LVAD implants, n = 8; BVAD implant, n = 1; TAH implant, n = 1), 58

patients (19.0%) were transplanted, and 27 patients (8.8%) died whilst awaiting cardiac transplantation. Causes of death were multiple organ failure (n = 8), sudden cardiac death or cardiogenic shock (n = 7), sepsis (n = 4), pneumonia (n = 1), others such as gastrointestinal complications or renal failure (n = 5), and unknown cause of death (n = 2).

Clinical and Biochemical Characteristics of Study Subgroups

Table I illustrates the characteristics of the patients who reached or did not reach the primary endpoint. The two groups were comparable with respect to various parameters, including hemodynamics and echocardiographic parameters. However, patients who reached the primary endpoint had a significant lower body weight and suffered more often from dilated cardiomyopathy and less often from ischemic heart disease than patients who did not reach the primary endpoint. In addition, the listing status was more often 'urgent' or 'high urgent' than in patients who did not reach the primary endpoint. With the exception of the use of inotropes, baseline medication was similar between both groups.

Table II illustrates GFR and biochemical parameters according to in- and outpatient state. GFR, CRP, and several parameters of mineral metabolism differed significantly between groups. Table III presents the biochemical results according to the different subgroups of the composite endpoint. Highly significant differences were observed for Na, Mg, PTH, $1,25(OH)_2D$, CRP, FGF-23, and TIMP. In detail, compared to patients who did not reach the primary endpoint all subgroups of patients who reached a component of the primary endpoint had lower Na, and $1,25(OH)_2D$ concentrations at baseline. In addition, Mg concentrations were lower in these patients; with the exception of patients who needed MCS support. Concentrations of CRP were significantly higher in all subgroups of the composite endpoint, whereas FGF-23 and TIMP values were only enhanced in patients with MCS implants and non-survivors, but not in transplanted patients. PTH concentrations showed mixed results with relatively

Table I. Characteristics of patients who reached and did not reach the primary endpoint.[1]

	Primary endpoint not reached n = 203	Primary endpoint reached n = 102	P-value
Age (years)	56.5 ± 0.7	54.2 ± 1.3	0.368
Gender (%males)	81.3	76.5	0.366
Weight (kg)	80.9 ± 0.9	73.1 ± 1.4	< 0.001
Height (cm)	175 ± 1	174 ± 1	0.289
Time on waiting list (days)	275 ± 47	230 ± 82	0.633
Urgent/high urgent listing (%)	5.4	35.4	0.001
LVEF (%)	30.1 ± 0.7	29.4 ± 1.2	0.558
LVEDD (mm)	70.0 ± 0.85	68.8 ± 1.6	0.460
Cardiac index (l/min/m^2)	1.98 ± 0.03	2.01 ± 0.06	0.693
Glomerular filtration rate (ml/min/1.73m^2)	56.0 ± 19.6	60.9 ± 26.0	0.094
Diagnosis			
Dilated cardiomyopathy (%)	38.4	56.9	0.003
Ischemic heart disease (%)	49.8	33.3	0.004
Others (%)	11.8	9.8	0.374
Concomitant diagnoses			
Previous thoracic surgery (%)	84.7	68.6	0.002
Diabetes mellitus (%)	27.2	24.8	0.306
Chronic kidney disease stage > III (%)	8.4	8.8	0.531
Medication			
Potassium sparing diuretics (%)	68.7	64.3	0.265
Loop diuretics (%)	94.0	96.9	0.216
Thiazid diuretics (%)	32.3	28.6	0.301
ACE inhibitors (%)	78.1	72.1	0.163
ß-blockers (%)	89.1	84.7	0.182
Antiarrhythmics (%)	31.2	42.2	0.165
Inotropes (%)	7.4	19.2	0.004

[1]Continuous variables are given as mean ± SEM; the primary endpoint was a composite of the need of mechanical circulatory support, transplantation, or death.

Table II. Biochemical parameters of in- and outpatients (mean ± SEM).

	Outpatients N = 259	Inpatients N = 46	P value
Glomerular filtration rate (ml/min/m^2)	56.1 ± 1.4	65.6 ± 3.6	0.016
Sodium (mmol/l)	138.2 ± 0.2	136.9 ± 0.6	0.052
Magnesium (mmol/l)	0.90 ± 0.01	0.87 ± 0.02	0.402
Calcium (mmol/l)	2.30 ± 0.02	2.27 ± 0.02	0.147
Inorganic phosphate (mmol/l)	1.16 ± 0.02	1.08 ± 0.06	0.07
NTproBNP (pmol/l)	470 ± 73	430 ± 51	0.582
Parathyroid hormone (pmol/l)	8.63 ± 0.42	3.66 ± 2.97	< 0.001
25(OH)D (nmol/l)	34.3 ± 2.5	23.5 ± 4.5	0.018
1,25(OH)$_2$D (pmol/l)	65.8 ± 2.6	44.2 ± 3.3	< 0.001
FGF-23 (RU/ml)	755 ± 175	608 ± 214	0.595
C-reactive protein (mg/dl)	1.10 ± 0.12	2.47 ± 0.64	0.042
TNF-α (pg/ml)	10.8 ± 0.4	11.9 ± 0.9	0.258
TIMP-1 (ng/ml)	163 ± 4	169 ± 13	0.638

Abbreviations: NTproBNP, n-terminal propeptide of brain natriuretic peptide; 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; FGF-23, fibroblast growth factor-23; TNF, tumor necrosis factor; TIMP, tissue inhibitor of metalloproteinases.

low values in patients receiving MCS support or transplantation and high values in non-survivors.

Risk Score Assessment of Clinical Outcome

We used the median of each of the aforementioned biochemical parameters as cut-off value to assess predictors of the primary endpoint. Table IV illustrates that Na, Mg, PTH, 1,25(OH)$_2$D and FGF-23 were all independently related to the composite endpoint, whereas Ca, PO_4, CRP, and TIMP were not significantly related to the composite endpoint (data not shown). Results did not change substantially when transplanted patients were censored (Table V).

We then evaluated a primary endpoint score as follows: I (Na < 138 mmol/l) + I (Mg < 2.11 mmol/l) + I (PTH < 6.1 pmol/l) + I (1,25(OH)$_2$D < 58.7 pmol/l) + I (FGF-23 > 204 RU/ml), whereby I (X) denotes the indicator function being equal to 1 if X holds and 0 otherwise. Figure 1 demonstrates that our score was able to discriminate satisfactorily between patients who reached and did not reach the primary endpoint. In patients who scored 5 points (6.5% of the study cohort) the primary endpoint was reached by 89.5%, whereas in patients with a score of zero (8.9% of the study cohort) the primary endpoint was reached in only 3.8%. The area under the ROC curve was 0.79 (95% CI: 0.73–0.84) (P < 0.001). By using a cut-off value of 3 points, sensitivity was 81.8% and specifity was 61.7%. With this cut-off value, the positive predictive value was 52.3% and the negative predictive value was 86.2%.

Table III. Biochemical parameters of the study cohort by clinical outcome (mean ± SEM).

	Event-free Survivors n = 203	MCS implantation N = 17	Transplanted n = 58	Non Survivors N = 27	P value
Sodium (mmol/l)	138.6 ± 0.3	136.1 ± 0.9	137.1 ± 0.5	135.7 ± 0.8	< 0.001
Magnesium (mmol/l)	0.90 ± 0.01	0.92 ± 0.04	0.81 ± 0.01	0.86 ± 0.03	< 0.001
Calcium (mmol/l)	2.31 ± 0.02	2.29 ± 0.04	2.29 ± 0.02	2.21 ± 0.08	0.023
Inorganic phosphate (mmol/l)	1.15 ± 0.02	1.12 ± 0.08	1.28 ± 0.03	1.10 ± 0.06	0.001
NTproBNP (pmol/l)	450 ± 53	390 ± 104	410 ± 49	676 ± 130	0.166
Parathyroid hormone (pmol/l)	8.93 ± 0.42	6.83 ± 1.26	5.88 ± 0.74	9.66 ± 1.89	0.001
25(OH)D (nmol/l)	34.5 ± 2.5	22.8 ± 2.5	25.8 ± 3.0	33.8 ± 4.5	0.077
1,25(OH)$_2$D (pmol/l)	69.8 ± 2.8	46.8 ± 9.0	47.5 ± 2.3	47.8 ± 6.8	< 0.001
FGF-23 (RU/ml)	564 ± 120	2088 ± 1627	492 ± 150	2416 ± 1245	< 0.001
C-reactive protein (mg/dl)	0.80 ± 0.08	2.76 ± 1.29	2.10 ± 0.41	3.28 ± 0.98	< 0.001
TNF-α (pg/ml)	10.6 ± 0.4	11.3 ± 1.7	11.8 ± 0.9	13.4 ± 1.3	0.048
Creatinine (μmol/l)	132 ± 4	131 ± 15	115 ± 5	148 ± 9	0.002
Bilirubin (μmol/l)	15.4 ± 0.9	16.8 ± 2.9	13.9 ± 1.2	18.1 ± 0.34	0.343
MMP-9 (ng/ml)	521 ± 21	399 ± 72	551 ± 38	597 ± 80	0.255
TIMP-1 (ng/ml)	154 ± 4	339 ± 152	158 ± 8	235 ± 20	< 0.001

Abbreviations: NTproBNP, n-terminal propeptide of brain natriuretic peptide; 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; FGF-23, fibroblast growth factor-23; TNF, tumor necrosis factor; MMP, matrix metalloproteinases; TIMP, tissue inhibitor of metalloproteinases.

Table IV. Logistic regression analysis of independent predictors of the primary endpoint.[1]

	Univariate analysis HR 95% CI	Multivariate analysis HR 95% CI	P value
Sodium (< 138 mmol/l)	3.116 (1.880–5.166)	1.947 (1.240–3.058)	0.004
Magnesium (< 0.87 mmol/l)	3.228 (1.951–5.341)	1.988 (1.255–3.150)	0.003
PTH (< 6.1 pmol/l)	2.540 (1.550–4.151)	1.992 (1.268–3.128)	0.003
$1,25(OH)_2D$ (< 58.7 pmol/l)	3.791 (2.268–6.338)	1.950 (1.213–3.137)	0.006
FGF-23 (> 204 RU/ml)	2.643 (1.597–4.375)	1.948 (1.216–3.122)	0.006

[1]The primary endpoint was a composite of the need of mechanical circulatory support, transplantation, or death. Additional parameters that were included in the multivariate analysis (but did not show statistical significance) are glomerular filtration rate, serum Ca, serum PO_4, C-reactive protein, tissue inhibitor of metalloproteinases, and the logarithmic transformed propeptide of brain natriuretic peptide.

Discussion

This study demonstrates that derangements in parameters of mineral metabolism are more pronounced in end-stage heart failure patients who reach a composite endpoint of different clinical events within 90 days of blood sampling than in patients who did not reach this composite endpoint. Based on these results, it was possible to develop a score which could estimate clinical outcome. Results did not change substantially when transplanted patients were censored.

It is well known that disturbances in mineral metabolism adversely affect the myocardium and may contribute to its failure as a pulsatile muscular pump (16). It is also well known that hyponatremia and hypomagnesemia are prevalent in end-stage CHF (6,7). Whereas hyponatremia is already considered an important risk factor for poor outcome (17), Mg has only rarely been considered as independent risk factor for poor outcome in CHF patients. However, Mg is essential for normal functioning of the cardiovascular system and hypomagnesemia is a common condition in hospitalized patients (18). In acutely ill patients, the mortality rate of those with hypomagnesemia was double that of the normomagnesemic group (19). Notably, in our patients not only hyponatremia (serum Na < 135 nmol/l) and hypomagnesemia (serum Mg < 0.70 mmol/l) but also less pronounced disturbances (Na < 138 mmol/l; Mg < 0.87 mmol/l) in these minerals are already associated with poor outcome. Similar to Mg, the significance of disturbances in Ca and PO_4 metabolism for clinical outcome in CHF is not well understood. Our data demonstrate that hormones responsible for the regulation of these two minerals such as $1,25(OH)_2D$, PTH, and FGF-23 predict clinical outcome better than serum Ca and PO_4 levels itself. Besides its calcemic effects, $1,25(OH)_2D$ exerts several effects on the immune system, the cardiovascular system and the nerve system (20). These non-classical vitamin D actions might at least in part contribute to the protective effects on event-free survival. It was a surprising result that low -and not high- PTH levels independently predicted poor outcome in our cohort of end-stage CHF patients. A similar phenomenon has been observed in chronic kidney disease patients, where PTH levels which are usually considered as normal were related to poor clinical outcome (21). Others have also found surprisingly low PTH levels in frail chronically bedridden patients with vitamin D deficiency (22). PTH can improve cardiac function by increasing heart rate, myocardial blood flow and cardiac output (23), which might explain some protective effects of high PTH levels. FGF-23 is a newly recognized phosphaturic hormone (12). Recently, it has been demonstrated that high FGF-23 concentrations in chronic kidney disease are associated with poor clinical outcome (14). Our results indicate a similar effect in end-stage CHF patients. Note that FGF-23 and $1,25(OH)_2D$ levels are interrelated since high FGF-23 levels suppress $1,25(OH)_2D$ (24).

Since the score-based biochemical parameters are very sensitive to physiological and pathophysiological metabolic stimulations, it is reasonable that these can predict mid-term clinical outcome. As the CHF clinical condition change can occur rapidly, it

Table V. Logistic regression analysis of parameters of mineral metabolism as predictors of a composite endpoint of mechanical circulatory support or death.

	Univariate analysis HR 95% CI	Multivariate analysis HR 95% CI	P value
Sodium (< 138 mmol/l)	2.878 (1.477–5.607)	2.114 (1.063–4.207)	0.033
Magnesium (< 0.87 mmol/l)	2.170 (1.168–4.029)	2.038 (1.089–3.815)	0.026
PTH (< 6.1 pmol/l)	1.642 (0.899–3.000)	1.701 (0.904–3.201)	0.100
$1,25(OH)_2D$ (< 58.7 pmol/l)	2.813 (1.466–5.398)	1.682 (0.843–3.355)	0.140
FGF-23 (> 204 RU/ml)	2.947 (1.513–5.742)	2.447 (1.191–5.026)	0.015

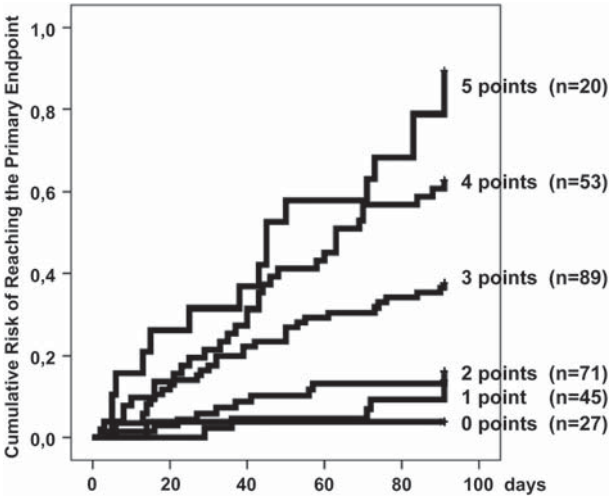

Figure 1. Kaplan-Meier estimates of the incidence of the Primary Endpoint broken down by the 5 score groups of deranged mineral metabolism. The primary endpoint was a composite of the need of mechanical circulatory support, transplantation, or death. Log rank test $P < 0.001$ between groups.

is also understandable that the score was a better predictor of event free survival than the initial time spent on the waiting list. It is also noteworthy that at baseline, clinical parameters such as hemodynamic and echocardiographic parameters were on average still similar between survivors and non-survivors. Interestingly, parameters of systemic inflammation such as CRP and TNF-α, and NTproBNP did not independently predict event-free survival. Note that patients listed 'high urgent' for transplantation are in poor clinical condition and are hospitalized. This may explain the fact that some biochemical parameters differed significantly between in- and outpatients.

For routine use in clinical practise, our risk score needs further validation in additional study cohorts. Generally however, a score based on several parameters of mineral metabolism may be used (i) for optimising donor heart allocation, (ii) for deciding on the necessity of MCS support in the near future, (iii) for end-stage CHF patients and/or their relatives for assessing the patient's chance of event-free survival in the near future, and (iv) in the search of new or additional treatment strategies. Future studies have to clarify whether specific drugs or nutritional supplements are able to improve mineral derangements and clinical outcome.

Our study has both, strengths and limitations. Strengths are the relatively large sample size, a relatively short time period for patient recruitment, the homogenous group of patients and the use of sensitive biochemical parameters of mineral metabolism for the calculation of risk scoring. One limitation is the fact that the inclusion of other biochemical parameters of mineral metabolism, e.g. parameters of zinc and iron status, which also show derangements in CHF-patients (25,26), may have improved sensitivity and specifity of the score rating. Thus, the scoring should be refined in future investigations. Another limitation of our analysis is the fact that we did not assess established clinical risk scores such as the Seattle score (27) or the APACHE score (28). Future studies should therefore investigate whether a combined risk score of biochemical and clinical parameters is able to enhance the predictive value on the primary endpoint.

In conclusion, our data demonstrate that in addition to the well-known disturbed Na metabolism, derangements in parameters of Ca, PO_4, and Mg metabolism are also prevalent in end-stage CHF patients and predict their clinical outcome.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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