Intact fibroblast growth factor 23 tested by a fully automated assay: clinical correlates and prognostic value in chronic systolic heart failure

Giuseppe Vergaro (✉ vergaro@ftgm.it)

Fondazione Toscana Gabriele Monasterio

Annamaria Del Franco

Scuola Superiore Sant'Anna

Francesco Gentile

Fondazione Toscana Gabriele Monasterio

Vincenzo Castiglione

Fondazione Toscana Gabriele Monasterio

Alberto Aimò

Scuola Superiore Sant'Anna

Federica Saponaro

University of Pisa

Silvia Masotti

Fondazione Toscana Gabriele Monasterio

Concetta Prontera

Fondazione Toscana Gabriele Monasterio

Niccolò Fusari

Fondazione Toscana Gabriele Monasterio

Michele Emdin

Scuola Superiore Sant'Anna

Claudio Passino

Scuola Superiore Sant'Anna

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Abstract

Background Fibroblast growth factor-23 (FGF23) has been associated to left ventricular (LV) hypertrophy and heart failure (HF) severity. We aimed to investigate clinical correlates and prognostic value of intact FGF23 (iFGF23) in HF patients.

Methods Patients with systolic HF (left ventricular ejection fraction - LVEF<50%) were prospectively enrolled. iFGF23 was tested with a fully automated immuno-chemiluminescent assay. Patients were divided into iFGF23 tertiles and followed-up for all-cause death, cardiac death, and the composite of all-cause death and HF hospitalizations.

Results We enrolled 150 patients (82% males; median age 65 years). First, second, and third iFGF23 tertiles were <35.2 pg/mL, 35.2-50.9 pg/mL, and >50.9 pg/mL. Patients in the upper iFGF23 tertile had lower LVEF ($p=0.014$), higher NT-proBNP ($p=0.001$), and lower peak VO_2 ($p<0.001$). Phosphate, estimated glomerular filtration rate (eGFR), and LV mass index were independently associated to iFGF23 (all $p<0.05$). Patients in the upper tertile were at higher risk of all-cause death ($p=0.001$), cardiac death ($p=0.001$), and of the composite of all-cause death and HF hospitalizations ($p=0.003$). iFGF-23 was an independent predictor of all the end-points after adjustment for age, LVEF, eGFR, and NT-proBNP.

Conclusions Circulating iFGF23 is associated with renal dysfunction, disease severity and outcome in systolic HF.

Introduction

Fibroblast growth factor 23 (FGF23) is a peptide hormone mainly synthesized in the bone, regulating phosphate balance by blocking renal tubular phosphate reabsorption and inhibiting the synthesis of 1,25-dihydroxyvitamin D [1]. Moreover, FGF23 has been shown to have pleiotropic effects beyond the regulation of calcium-phosphate homeostasis [2]. FGF23 receptors are indeed expressed in the heart, and several experimental and clinical studies support a role of FGF23 in the development of left ventricular (LV) hypertrophy, fibrosis, and dysfunction [3-6] in different settings, including chronic kidney disease, mostly through an interplay with the renin-angiotensin-aldosterone system (RAAS) [3]. The combination of increased FGF23 and low Klotho – a FGF23 cofactor – levels is associated with a higher risk of cardiovascular death or heart failure (HF) hospitalization in subjects with stable ischemic heart disease. Similarly, the elevation of FGF23 is associated with a significantly increased risk of incident HF in hypertensive populations [7,8].

Over the past years, FGF23 has emerged as a possible HF biomarker [9]. For example, in the BIOlogy Study to Tailored Treatment in Chronic HF (BIOSTAT-CHF) study, the elevation of FGF23 identified a subset of HF patients with more severe disease and is associated to impaired up-titration of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) [10]. While previous studies had shown that FGF23 is independently associated with cardiovascular mortality and with the composite endpoint of death or heart transplantation in patients with systolic HF [9,11], a recent *post-hoc* analysis of

the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) has questioned the predictive power of FGF23 [12].

Furthermore, all the studies published so far have reported the clinical value of FGF23 tested with enzyme-linked immunosorbent assays directed to either C-terminal FGF23 (cFGF23) or to the intact, biologically active hormone (iFGF23). A novel, fully automated FGF23 assay measuring selectively iFGF23 has become available [13], but the clinical significance of iFGF23 in patients with HF remains to be elucidated.

We aimed to assess correlates and prognostic value of iFGF23, tested with an automated assay, in a fully characterized cohort of patients with systolic HF.

Materials And Methods

Study population

We enrolled 150 consecutive patients with systolic HF (left ventricular ejection fraction - LVEF <50%), in a tertiary referral centre for HF (Fondazione Toscana Gabriele Monasterio, Pisa, Italy), between June 2015 and December 2016. All patients were on stable guideline-recommended HF therapy since at least 2 months. Diagnosis of chronic HF was made according to contemporary European Society of Cardiology guidelines [14]. Exclusion criteria were acute coronary syndrome or HF decompensation, coronary artery revascularization or cardiac resynchronization therapy within 3 months before enrolment. Patients underwent resting 12-lead electrocardiogram, biohumoral characterization, echocardiography and cardiopulmonary exercise testing (CPET). Standard 2D echocardiography was performed to evaluate LV geometry, and indices of systolic and diastolic function, according to standard procedures [15].

The study protocol conforms to the 1975 Declaration of Helsinki and was approved by the Ethical Committee of the Outer North West Area, Tuscany (Italy). Written informed consent was obtained from each patient.

Biohumoral assays

Blood samples were drawn after an overnight fasting period and a 20-minute supine rest [16], and then stored at -80°C until assays were performed. Plasma renin activity (PRA) and aldosterone were measured using a radioimmunoassay method (DiaSorin S.r.l., Saluggia, Italy) [17,18]. Plasma epinephrine and norepinephrine were evaluated by means of high-performance liquid chromatography technique using the electrochemical detector CLC 100 (Chromsystems GmbH, München, Germany) [19]. N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP) was measured with an electrochemiluminescence immunoassay monoclonal method using the Cobas e411 platform (Roche Diagnostics Italia, Monza, Italy) [20]. 25 hydroxy-vitamin D3 (25OHD) was measured by isotope dilution (HPLC-MS/MS), by using the MSMS vitamin D Kit from PerkinElmer (Waltham, MA, USA). Agilent 1290 Infinity UHPLC system was

used (Santa Clara, CA, USA), including autosampler, binary pump, and column oven, coupled to an AB Sciex API 4000 triple quadrupole mass spectrometer (Concord, ON, Canada), equipped with an APCI source. Chromatography was performed by a PerkinElmer Brownlee Supra C18 3 μ m, 50×2.1 mm HPLC column, protected by a PerkinElmer Brownlee Supra C18 Guard Column. Plasma parathyroid hormone (PTH) was measured by the third-generation assay 1-84 PTH assay, chemiluminescent immunoassay (DiaSorin, Saluggia, Italy). Finally, for FGF23 evaluation, an automated iFGF23 immuno-chemiluminescent sandwich assay (DiaSorin, Saluggia, Italy; LoD <10 ng/L, intra-assay CV <3%, inter-assay CV <7%) was employed [13].

All these assays were performed according to manufacturer instructions. Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Survival analysis and endpoints

Follow-up was performed every 3 to 6 months unless otherwise clinically required. Data were collected by two independent interviewers directly from patients, relatives, or general practitioners, while the time and the precise cause of death were retrieved from death certificates, *post-mortem* reports, and general practitioners. The primary endpoint was all-cause death, while the secondary endpoints were cardiac death (including sudden cardiac death and death due to HF progression or acute myocardial infarction) and the composite of all-cause death and HF hospitalizations. Patients were censored after the last medical contact.

Statistical analysis

After evaluation for normality by Kolmogorov-Smirnov test, normally distributed variables were reported as mean $\pm$ standard deviation while skewed variables as median and interquartile interval (IQI). Categorical data were reported as frequencies. According to variable distribution, ANOVA or Kruskal-Wallis test were used for multiple comparisons among groups, with *post hoc* Dunn-Bonferroni correction for pairwise comparisons. χ^2 or Fisher test were adopted for qualitative variables. Linear regression models were employed to evaluate correlates of iFGF23 levels, including clinical parameters (age, gender, body mass index - BMI, New York Heart Association - NYHA - class), laboratory (eGFR, haemoglobin, phosphate, PTH, 25OHD, calcium, aldosterone, PRA and catecholamine levels), and echocardiography parameters (LVEF, pulmonary artery systolic pressure - PAPs, LV mass index – LVMI, E/e' ratio). All variables with $p < 0.05$ at univariate analysis were included in a multivariate regression model.

For survival analysis, the first iFGF23 tertile was considered as reference category. Kaplan-Meier method and Log-Rank statistics (Mantel-Cox) were used to estimate all-cause mortality and cardiac death, according to iFGF23 tertiles. A multivariable Cox proportional hazard model was built to manage possible confounders, selected *a priori* and including age, eGFR, LVEF and NT-proBNP. Net reclassification

improvement (NRI, with risk categories set at <10%, 10-30% and >30%) and the integrated discrimination improvement (IDI) were calculated to assess reclassification.

Statistical analysis was performed using SPSS (IBM Statistics, version 26.0, 2019). A two-tailed p value ≤ 0.05 was considered significant.

Results

Baseline characteristics and comparison among iFGF23 tertiles

We enrolled 150 consecutive patients with systolic HF (median LVEF 32%, IQI 27-38%). Median age was 65 years (54-74 years), 82% were males, and 72% were in NYHA class I-II. Renal function was mainly preserved (eGFR 73 ± 24 mL/min/1.73 m²). Further, NT-proBNP plasma levels (953 ng/L, 354-2024 ng/L) demonstrated a moderate extent of neurohormonal activation, despite the use of an optimal medical therapy (87% of population treated with β -blockers, 61% with ACEi, 31% with ARBs and 61% with mineralocorticoid receptor antagonists - MRAs).

Median iFGF23 was 41.8 pg/mL (30.6-55.6 pg/mL) and the first, second, and third tertile were <35.2 pg/mL, 35.2-50.9 pg/mL, and >50.9 pg/mL, respectively. Baseline characteristics of the overall population and differences among iFGF23 tertiles are shown in detail in **Table 1** and **Figure 1**. Compared to patients in the first tertile, patients in the third tertile of iFGF23 showed lower maximal oxygen consumption at CPET and lower LVEF at echocardiography. In addition, compared to the first and second tertile of iFGF23, patients in the upper tertile showed higher levels of NT-proBNP and lower eGFR. Patients in the upper tertile of iFGF23 showed higher PTH than patients with lower levels of iFGF23, while no significant difference could be found for phosphate or 25OHD.

Table 1

Baseline characteristics of the overall population and by tertiles of intact fibroblast growth factor 23 (iFGF23).

	Overall (n=150)	iFGF23 <35.2 pg/mL (n=50)	iFGF23 35.2-50.9 pg/mL (n=50)	iFGF23 >50.9 pg/mL (n=50)	p value (trend)
Age, years	65 (54-74)	63 (54-72)	68 (54-76)	67 (57-75)	0.325
Male, n (%)	123 (82)	39 (78)	43 (86)	41 (82)	0.501
BMI, Kg/m ²	26.2 (23.9-29.8)	26.0 (23.6-29.1)	26.2 (24.5-26.7)	26.8 (23.0-31.5)	0.844
NYHA class					0.152
I	39 (26)	17 (34)	13 (26)	9 (18)	
II-III	111 (74)	33 (66)	37 (74)	41 (82)	
Atrial fibrillation, n (%)	21 (28)	5 (10)	12 (24)	4 (8)	0.036
Peak VO ₂ , mL/(kg·min)	13.6 (10.8-18.0)	17.1 (12.4-21.3)	14.2 (11.1-18.4)	12.3 (10.0-13.9)*	<0.001
LVEF, %	32 (27-38)	35 (30-39)	35 (28-40)	30 (25-38)*†	0.014
LVMI, g/m ²	129 (112-157)	123 (109-143)	132 (120-164)	137 (115-178)	0.103
PAPs, mmHg	35 (29-40)	32 (29-38)	35 (29-40)	36 (30-43)	0.102
E/e'	12 (8-16)	9 (7-12)	13 (10-16)	13 (7-18)	0.089
Haemoglobin (g/dL)	13.6 (1.5)	13.9 (1.1)	13.4 (1.6)	13.7 (1.7)	0.335
eGFR, mL/min/1.73 m ²	73±24	86±20	75±20*	59±23*†	<0.001
PTH, pg/mL	19.6 (14.3-27.9)	18.4 (12.3-25.4)	17.8 (13.2-25.1)	22.1 (16.7-35.0)*†	0.003
Phosphate, mg/dL	3.5 (3.0-4.1)	3.4 (3.0-3.9)	3.5 (3.0-4.0)	3.7 (3.1-4.4)	0.267
Calcium, mg/dL	9.00 (8.75-9.20)	9.00 (8.70-9.23)	8.90 (8.70-9.10)	9.10 (9.00-9.30)†	0.004
25-hydroxyvitamin D3, ng/mL	16.26 (9.40-24.49)	15.19 (7.60-21.50)	20.53 (13.63-25.97)	15.83 (9.09-25.44)	0.078
NT-proBNP, ng/L	953 (354-2024)	686 (219-1349)	822 (376-1567)	1680 (635-3285)*†	0.001
PRA, ng/mL/h	1.31 (0.30-3.94)	0.71 (0.20-2.40)	1.13 (0.21-3.15)	2.37 (0.75-7.44)*	0.003

Aldosterone, ng/dL	137.8 (89.4-209.4)	137.8 (98.9-190.7)	105.5 (71.7-179.6)	168.8 (91.4-322.2) [†]	0.027
Epinephrine, ng/L	22 (10-52)	18 (10-45)	18 (10-51)	27 (10-60)	0.575
Norepinephrine, ng/L	404 (283-595)	388 (242-621)	377 (241-523)	510 (316-628)	0.126
ACEi, n (%)	92 (61)	33 (66)	30 (60)	29 (58)	0.557
ARBs, n (%)	46 (31)	17 (34)	12 (24)	17 (34)	0.493
Beta blockers, n (%)	130 (87)	43 (86)	44 (88)	43 (86)	0.708
MRAs, n(%)	92 (61)	30 (60)	28 (56)	34 (68)	0.616
Diuretics, n (%)	104 (69)	31 (62)	35 (70)	38 (76)	0.451

ACEi, angiotensin-converting-enzyme inhibitors; ARBs, Angiotensin II receptor blockers; BMI, body mass index; eGFR, estimated Glomerular Filtration Rate; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MRAs: mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAPs, pulmonary artery systolic pressure; PRA, plasma renin activity; PTH, parathormone.

*P<0.05 vs. first tertile of FGF23, †P<0.05 vs. second tertile of FGF23.

Clinical and biohumoral correlates of iFGF23

Univariate predictors of iFGF23 are listed in **Table 2**. When all univariate predictors were pooled in a multivariable analysis, only eGFR (standardized β =−0.422, p<0.001), phosphate (standardized β =0.179, p=0.024) and LVMI (standardized β =0.188, p=0.033) were independently correlated to iFGF23 levels.

Table 2

Clinical correlates of intact fibroblast growth factor 23 (iFGF23)

	Non-standardized B	95% confidence interval for B	Standardized Beta coefficients	P value
LVEF	0.007	-0.003 to 0.018	0.137	0.171
NYHA Class	-0.044	-0.148 to 0.060	-0.073	0.404
PASP	0.005	-0.002 to 0.012	0.128	0.147
LVMI	0.002	0.000 to 0.004	0.188	0.033
NT-proBNP	0.000	0.000 to 0.000	0.126	0.248
eGFR	-0.008	-0.011 to -0.004	-0.422	<0.001
PTH	-0.001	-0.007 to 0.004	-0.039	0.672
Phosphate	0.090	0.012 to 0.167	0.179	0.024
PRA	0.035	-0.021 to 0.090	0.113	0.216
Aldosterone	-0.017	-0.121 to 0.086	-0.030	0.739
Norepinephrine	0.015	-0.105 to 0.135	0.019	0.808

Univariate predictors of iFGF23 concentration have been pooled into a multivariable model. Only LVMI, eGFR, and phosphate were independently associated to iFGF23. eGFR, estimated Glomerular Filtration Rate; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; PRA, plasma renin activity; PTH, parathormone.

Prognostic impact of iFGF23 on mortality

During a median follow-up of 70 months (range 2-135), 25 (17%) patients died, 14 of them due to cardiac causes; 24 HF hospitalizations were recorded. Decedents had higher iFGF23 than survivors (56.3 [44.4-88.3] pg/mL vs 39.6 [29.4-52.7] pg/mL, $p<0.001$). In unadjusted Cox proportional hazard model, iFGF23 levels significantly predicted all-cause death (HR=7.62, 95% CI [3.17-18.35]; $p<0.001$), cardiac death (HR=7.43, 95% CI [2.29-24.06]; $p=0.001$), and the composite of all-cause death and HF hospitalization (HR=5.39, 95% CI [2.52-11.52]; $p<0.001$). After multivariable adjustment including age, eGFR, LVEF and NT-proBNP, the association between iFGF23 and outcome was maintained (all-cause death: HR=4.27, 95% CI [1.43-12.79], $p=0.009$; cardiac death: HR=3.29, 95% CI [0.76-14.29], $p=0.011$; all-cause death and HF hospitalization: HR=2.89, 95% CI [1.14-7.38], $p=0.026$). FGF23 also improved reclassification over NT-proBNP for the composite end-point (NRI=0.335, 95% CI [-0.050- 0.720], $p=0.088$; IDI=0.068, 95% CI [0.005-0.131], $p=0.034$). Furthermore, patients in the upper tertile of iFGF23 were at higher risk of 5-year all-cause (Log-rank 13.62, $p=0.001$) (**Figure 2a**), cardiac death (Log-rank 14.31, $p=0.001$) (**Figure 2b**) and of the

composite of all-cause death and HF hospitalization (Log-rank 11.85, $p=0.003$) (**Figure 2c**) compared to patients in the lower and middle tertile.

Discussion

In our fully characterized cohort of patients with stable HF, higher iFGF23, tested with a fully automated assay, was associated with clinical severity of the disease, as expressed by lower LV systolic function and higher circulating levels of NT-proBNP, and impaired functional capacity, demonstrated by lower peak VO_2 at CPET. Moreover, iFGF23 elevation identified patients at higher risk for all-cause and cardiac mortality, independently of NT-proBNP and other established markers, including renal function (**Figure 3**).

Correlates of iFGF23

FGF23 plays a key role in regulating phosphate homeostasis. Elevated FGF23 levels increase fractional phosphate excretion at kidney level and inhibit PTH synthesis and secretion by parathyroid cells [21]. On the other hand, phosphate itself is a major regulator of FGF23: dietary phosphate loading increases circulating FGF23 levels, whereas phosphate depletion decreases FGF23 expression [22]. The evidence of the independent association between iFGF23 and phosphate in our population is therefore supported by pathophysiological mechanisms of FGF23 regulation.

Renal function, assessed by eGFR, emerged as another independent predictor of iFGF23 in our study. The inverse correlation between eGFR and iFGF23 is likely due to both direct and indirect mechanisms, consisting in the reduced renal excretion of iFGF23 and increased phosphate levels, respectively, following decreasing renal function.

There is experimental evidence that FGF23 may enhance RAAS activity [23], although more recent clinical data are controversial [7]. An analysis from the Multi-Ethnic Study of Atherosclerosis (MESA) study could not demonstrate a relationship between iFGF23 and either circulating aldosterone or PRA in hypertensive patients [7]. Conversely, data from a large population with new onset or worsening HF have shown that aldosterone levels were independently associated with higher FGF23 [10]. This is the first study addressing the possible association between biohumoral indices of RAAS activation and iFGF23 in the setting of chronic HF. In our population, both aldosterone and PRA were associated to iFGF23 circulating levels at univariate analysis, but the association was lost after multivariate adjustment.

Stimulation of RAAS activity has been postulated as one of the mechanisms underlying the association between FGF23 and LV hypertrophy [5]. Available data also suggest that activated RAAS induces myocardial expression of FGF23 [24], that could in turn promote fibrosis-related pathways in fibroblasts and consequently cardiac remodelling and dysfunction [25]. Experimental studies show how transgenic mice with overexpression of a constitutively active FGF receptor-1 develop LV hypertrophy [26]. Further, FGF23 blockade reverses the hypertrophic growth of isolated myocytes *in vitro* and established LV hypertrophy *in vivo* [27]. We report here that LVMI is independently associated with iFGF23 in a cohort of

stable systolic HF patients. These findings could support the hypothesis that FGF23 is not only a biomarker of increased risk but acts as a direct endocrine and paracrine player in the pathophysiology of HF.

iFGF23 and outcome in stable HF patients

Our findings that iFGF23 is an independent predictor of outcome in patients with HF is in line with previous evidence reporting FGF23 as a correlate of HF-related outcome, in patient with or without kidney disease [7], as well as a predictor of cardiovascular death in a small HF cohort [11]. Recently, data from 382 patients enrolled in the TIME-CHF (Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive Heart Failure) cohort have questioned the role of FGF23 in risk stratification [12]. Still, this analysis included patients with more severe disease (no patient in NYHA class I vs. 26% in our population), and both cFGF23 and iFGF23 were tested with commercially available ELISA assays. We used rather a fully automated immunoassay for iFGF23 that is approved for clinical use and shows excellent analytical characteristics, allowing standard results and references. In addition, this assay measures the intact form of (iFGF23), showing a stronger biological activity than cFGF23 [28]. Furthermore, all blood samples were performed at the same time of the day, to avoid potential circadian variations of FGF23 levels between patients, and testing included a full characterization of RAAS activation as well as of phosphate and calcium metabolism.

Significance

FGF23 is increasingly recognized as a marker and a mediator of disease progression in HF. Our findings support the role of iFGF23 as a player in cardiac remodelling following renal dysfunction and a tool for risk stratification in HF patients. Characterization of the clinical significance of iFGF23 is of great relevance given the availability of different pharmacological approaches for FGF23 blockade. These include inhibitors of gastrointestinal sodium/hydrogen exchanger isoform 3 such as tenapanor [29], and cinacalcet, a calcimimetic agent that has been shown to reduce both serum FGF23 levels and rates of cardiovascular death and major cardiovascular events in haemodialysis patients [30]. Finally, burosumab, a monoclonal antibody targeting FGF23, has been recently tested in patients with X-linked hypophosphatemia [31].

Limitations

Serial measurements of iFGF23 have not been performed in the present study, so changes in iFGF23 during the follow-up and their influence on patient outcome can not be assessed. Moreover, we report data from a single tertiary centre, possibly limiting the generalizability of our findings. Considering the limited number of enrolled patients, a re-classification of FGF23 tertiles based on LVEF could not be performed.

Conclusion

Circulating iFGF23, assessed with a novel fully automated assay, is associated with renal dysfunction, disease severity and outcome in a population of stable systolic HF patients. The relevance of iFGF23 as a marker in this clinical setting is supported by its biological role in prohypertrophic and profibrotic pathways, mostly activated both in renal and cardiac failure and sustaining cardiac remodelling, all this suggesting FGF23 as a possible therapeutic target in HF patients.

Abbreviations

25OHD, 25 hydroxy-vitamin D3

ACEi, angiotensin-converting enzyme inhibitors;

ARBs, angiotensin receptor blockers;

BMI, body mass index;

cFGF23, C-terminal fraction of FGF23;

eGFR, estimated glomerular filtration rate;

FGF23, fibroblast growth factor-23;

HF, heart failure;

iFGF23, intact FGF23;

LV, left ventricular;

LVEF, left ventricular ejection fraction;

LVMI, left ventricular mass index;

MRAs, mineralocorticoid receptor antagonists;

NT-proBNP, N-terminal fraction of pro-B-type natriuretic peptide;

NYHA, New York Heart Association;

PASP, pulmonary artery systolic pressure;

PRA, plasma renin activity;

PTH, parathyroid hormone;

RAAS, renin-angiotensin-aldosterone system.

Declarations

Ethical approval and consent to participate

The study protocol conforms to the 1975 Declaration of Helsinki and was approved by the Institution's human research committee. Written informed consent was obtained from each patient.

Consent for publication

A written informed consent for publication of results of the present study was obtained from each patient.

Competing interest

There are no conflicts of interest to declare.

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Author contribution

The authors contributed in multiple roles. Giuseppe Vergaro: Conceptualization, Methodology, Visualization. Annamaria Del Franco: Investigation, Visualization, Writing- Original Draft. Francesco Gentile: Investigation, Visualization, Writing- Original Draft. Vincenzo Castiglione: Writing- Original Draft. Alberto Aimò: Writing-Review & Editing. Federica Saponaro: Investigation. Silvia Masotti: Investigation. Concetta Prontera: Resources, Writing-Review & Editing. Niccolò Fusari: Data curation, Validation. Michele Emdin: Supervision. Claudio Passino: Supervision.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the ongoing research for other items of interest in the same enlarged population, but are available from the corresponding author on reasonable request.

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Figures

Figure 1

Baseline characteristics of patients in each FGF23 tertile. Cardiorespiratory performance, laboratory examinations and echocardiography parameters of patients in the first (T1, <35.2 pg/mL), second (T2, 35.2-50.9 pg/mL) and third (T3, >50.9 pg/mL) iFGF23 tertile.

*P<0.05 vs. first tertile, †P<0.05 vs. second tertile. eGFR, estimated Glomerular Filtration Rate; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro B-type natriuretic peptide; PRA, plasma renin activity; PTH, parathormone.

Figure 2

FGF23 tertiles and outcome. Kaplan-Meier curves depicting rates of 5-year all-cause mortality (a), cardiac mortality (b) and of the composite of all-cause mortality and heart failure hospitalizations (c) according to iFGF23 tertiles.

Figure 3

Prognostic impact of FGF23 levels in patients with systolic heart failure (HF). In a cohort of HF patients with systolic dysfunction, higher iFGF23 levels (index of increased cardiac fibrosis and hypertrophy) were associated with clinical severity of the disease, as expressed by lower left ventricular systolic function, higher circulating levels of N- terminal pro-brain natriuretic peptide (NT-proBNP), lower oxygen consumption at cardiopulmonary exercise test and worsening of renal function. Moreover, iFGF23 elevation identified patients at higher risk for all-cause and cardiac mortality, and HF hospitalization.