# Serum Phosphate and Long-Term Outcome Among Patients With Stable Heart Failure

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**ABSTRACT**

**Background:** Elevated serum phosphate levels are associated with excess risk for cardiovascular mortality in patients with and without chronic kidney disease and with increased risk for incident heart failure. We determined the association of serum phosphate concentrations with disease severity and long-term outcome in patients with overt heart failure.

**Methods and Results:** Clinical and laboratory parameters of 974 ambulatory heart failure patients were evaluated. Prevalence of elevated phosphate levels (>4.5 mg/dL) was 5.8% in men and 6.0% in women. Phosphate was significantly correlated with disease severity as assessed by New York Heart Association class, left ventricular ejection fraction, and N-terminal pro-B-type natriuretic peptide ($P < .01$, respectively). Multivariate sex-stratified Cox regression analysis adjusted for various clinically relevant covariates revealed baseline phosphate to be independently associated with death from any cause or heart transplantation (HR 1.26 [95% CI 1.04−1.52]; $P < .001$). This relation was maintained in patients with and without chronic kidney disease. After categorization based on quartiles of phosphate levels, a graded, independent relation between phosphate and outcome was observed ($P$ for trend <.001).

**Conclusions:** We found a graded, independent relation between serum phosphate and adverse outcome in patients with stable heart failure. Also, serum phosphate was related to disease severity. These findings further highlight the clinical importance of serum phosphate in cardiovascular disease. (*J Cardiac Fail 2013;19:25−30*)

**Key Words:** Heart failure, phosphate, prognosis.

## Introduction

Phosphorus is essential for multiple and diverse biological functions such as energy production, membrane transport, and signal transduction.[1] Serum phosphate concentrations are regulated by a balance between dietary intake, absorption from the gastrointestinal tract, storage in the skeleton, and urinary phosphate excretion.[2,3] The most common cause of hyperphosphatemia is inadequate glomerular function. In patients with chronic kidney disease (CKD) higher serum phosphate levels are associated with increased cardiovascular disease (CVD) mortality.[4,5] Similar findings were also reported in patients with prior myocardial infarction (MI).[6] Furthermore, higher phosphate concentrations are related in a graded fashion to increased CVD risk in individuals with no CKD or CVD.[7]

Recent data suggest that serum phosphate even within the normal range is associated with greater left ventricular mass cross-sectionally, and with increased risk for heart failure prospectively in a large community-based sample of individuals without prior MI or CKD.[8] It is speculated that low vitamin D levels associated with higher serum phosphate,[9,10] vascular smooth muscle cell calcification,[11,12] and secondary hyperparathyroidism[4,13,14] may contribute to this relationship.

Hence, abnormal phosphate levels are consistently associated with adverse outcomes in patients with and without CKD and are related to incident heart failure in apparently healthy individuals.

The role of serum phosphate in patients with overt heart failure, however, is unknown. In this study, we examined the hypothesis that serum phosphate concentrations are

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associated with disease severity and long-term outcome by relating serum phosphate levels to New York Heart Association class, left ventricular ejection fraction (LVEF), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) cross-sectionally, and to transplant-free survival longitudinally in a large cohort of ambulatory heart failure patients.

## Methods

### Study Population

For this retrospective analysis we made use of a dataset consisting of 1302 consecutive Caucasian heart failure patients who were prospectively recruited for a clinical database between April 2000 and November 2009 at the specialized heart failure clinic of a tertiary referral center. Measurement of serum phosphate at baseline was available in 977 (75.0%) patients. Three patients with end-stage renal disease and exceptionally high serum phosphate levels (>6 mg/dL) were excluded. Hence, final analyses were restricted to 974 patients. Eligible patients were ≥18 years of age. The diagnosis of congestive heart failure (CHF) was based on the presence of current or previous symptoms or characteristic clinical signs, and evidence of left ventricular dysfunction. Patients were included irrespective of the underlying cause of heart failure and were treated according to prevailing CHF guidelines. Patients were followed until December 2010 (time of data censoring) or to the occurrence of death or heart transplantation, which constituted the combined endpoint. Death events were retrieved from the local mortality registry and from personal contacts with members of patient families. Follow-up information was available for 936 (96.1%) patients.

The study conformed with the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee of the Innsbruck Medical University. All patients gave written informed consent for participating in the study.

### Measurements

Blood was drawn in all patients at study entry. All laboratory variables were measured by a central laboratory that undergoes regular internal and external quality audits. Serum phosphate and serum calcium concentrations were measured in fasting blood samples using the standard colorimetric method (Roche Diagnostics, Mannheim, Germany) with an intra-assay coefficient of variation of 1.4%. Serum phosphate levels are given in mg/dL (to convert to millimoles per liter, multiply by 0.323). Glomerular filtration rate (GFR) was estimated using the simplified modification of diet in renal disease equation (estimated GFR [eGFR] [mL/min/1.73 $m^2$] = 186.3 × [serum creatinine]$^{-1.154}$ × age$^{-0.203}$ [× 0.742 if female]).[15] Estimated GFR values >200 mL/min/1.73 $m^2$ were set equal to 200 mL/min/1.73 $m^2$, according to Coresh et al.[16]

### Statistical Analysis

We used the Kruskal-Wallis and chi-square tests or 1-way analysis of variance to test for the differences in categorical or continuous factors, respectively, between different categories of serum phosphate. Pearson's partial correlation was used to assess cross-sectional relations between serum phosphate, heart failure severity, and kidney function. For this, NYHA classes were converted into a dichotomous variable (NYHA I/II vs III/IV).

Assessment of the prognostic relevance of serum phosphate for transplant-free survival was performed using sex-stratified Cox proportional hazards regression analyses. Models were run in both univariate and multivariate manner. Selection of variables for the multivariate Cox proportional hazards regression analyses was based on clinical relevance and differences in patient characteristics between quartiles of serum phosphate. The final model adjusted for age, body mass index (BMI), ischemic etiology, LVEF, heart rate, systolic blood pressure, NYHA class, eGFR, use of aldosterone antagonists and diuretics, and previous hospitalization for heart failure. NT-proBNP was not included because availability was restricted to 620 patients.

Additionally, a restricted maximum-likelihood optimizing penalized spline model was calculated to assess the shape of the relationship between serum phosphate level and risk for death or heart transplantation.[17] $P$ values <.05 were considered to indicate statistical significance. Statistical analysis was performed using the SPSS software package (SPSS 18.0 for Windows, SPSS Corp.).

## Results

Serum phosphate and calcium levels were approximately normally distributed in both sexes. Mean serum phosphate levels were almost 0.20 mg/dL lower in men (3.38 ± 0.6 mg/dL) than in women (3.55 ± 0.6 mg/dL) ($P < .001$). Prevalence of elevated serum phosphate (>4.5 mg/dL) was 5.8% in men and 6.0% in women. Corresponding numbers for low serum phosphate (<2.7 mg/dL) were 14.1% in men and 8.4% in women. Quartile ranges were similar among both men and women. Baseline characteristics according to quartiles of serum phosphate levels are displayed in Table 1.

### Cross-Sectional Relations Between Serum Phosphate, Heart Failure Severity, and Kidney Function

Serum phosphate was positively associated with NYHA class ($r = 0.104$; $P = .001$) and inversely related to LV-EF ($r = -0.131$; $P < .001$) in age- and sex-adjusted correlation analyses. Measurement of NT-proBNP at baseline was available in 620 patients (63.7%). In these patients, NT-proBNP was positively related to serum phosphate ($r = 0.191$; $P < .001$). An inverse association was observed between eGFR and serum phosphate ($r = -0.213$; $P < .001$).

### Relations Between Serum Phosphate and Heart Failure Outcomes

On follow-up (mean 40.4 months [95% CI 38.5−42.3]), 236 (24.1%) patients (57 women) died and 75 (7.7%) patients (17 women) underwent heart transplantation as their first event.

In univariate sex-stratified Cox regression analysis, serum phosphate (HR 1.56 [95% CI 1.32−1.84]; $P < .001$) was associated with increased risk for death or heart transplantation. The relation between higher serum phosphate levels and the endpoint remained robust even in patients (n = 797) with phosphate levels within the normal range (2.7−4.5 mg/dL) (HR 1.63 [95% CI 1.23−2.17]; $P = .001$), as well as in men (n = 725, HR 1.52 [95% CI 1.26−1.83]; $P < .001$) and women (n = 249, HR 1.74 [95% CI 1.16−2.61]; $P = .008$), and in patients <65 years

**Table 1.** Patient Characteristics

| | Serum Phosphate Levels | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Quartile 1 (≤2.97 mg/dl) | | Quartile 2 (2.98−3.41 mg/dl) | | Quartile 3 (3.42−3.84 mg/dl) | | Quartile 4 (≥3.85 mg/dl) | | |
| | n = 249 | | n = 240 | | n = 239 | | n = 246 | | |
| Variable | Median or % | IQR | Median or % | IQR | Median or % | IQR | Median or % | IQR | *P* |
| Demographic and clinical characteristics | | | | | | | | | |
| Age (years) | 63 | 55−71 | 61 | 51−69 | 62 | 51−69 | 61 | 50−68 | .184 |
| Gender (male) | 81.9% | | 77.1% | | 71.1% | | 67.5% | | .001 |
| LVEF (%) | 30 | 24−41 | 29 | 22−40 | 29 | 24−39 | 26 | 20−35 | <.001 |
| Heart rate (bpm) | 74 | 64−85 | 73 | 64−84 | 72 | 61−82 | 77 | 66−88 | .006 |
| Systolic BP (mmHg) | 130 | 120−140 | 120 | 110−140 | 125 | 110−140 | 120 | 100−130 | <.001 |
| BMI | 26.0 | 23.3−29.0 | 25.0 | 23.0−28.0 | 25.0 | 22.9−28.1 | 25.2 | 23.0−28.1 | .178 |
| NYHA class I | 30.9% | | 24.5% | | 24.3% | | 11.8% | | |
| NYHA class II | 45.9% | | 48.5% | | 48.1% | | 52.4% | | |
| NYHA class III/IV | 23.2% | | 27.0% | | 27.6% | | 35.8% | | <.001 |
| Hospitalization for heart failure (within the past 12 months) | 55.9% | | 60.6% | | 67.6% | | 74.1% | | <.001 |
| Ischemic etiology | 30.0% | | 28.5% | | 30.4% | | 33.3% | | .611 |
| A-Fib | 28.3% | | 23.5% | | 28.3% | | 26.6% | | .602 |
| Medical history | | | | | | | | | |
| Hypertension | 52.0% | | 42.5% | | 51.5% | | 40.9% | | .019 |
| Diabetes | 20.6% | | 17.5% | | 20.6% | | 24.1% | | .361 |
| Laboratory testing (serum) | | | | | | | | | |
| Calcium (mg/dL) | 9.4 | 9.1−9.8 | 9.4 | 9.1−9.8 | 9.4 | 9.1−9.8 | 9.5 | 9.2−9.8 | .301 |
| NT-proBNP (ng/L)* | 905 | 273−2183 | 1138 | 414−2496 | 1081 | 379−3133 | 2057 | 634−3953 | .001 |
| eGFR (ml/min/1.73) $m^2$) | 75.4 | 60.0−86.7 | 77.2 | 61.1−89.1 | 71.2 | 54.4−84.8 | 65.8 | 51.8−81.7 | <.001 |
| Medication | | | | | | | | | |
| ACE inhibitor/ARB | 81.9% | | 81.3% | | 79.5% | | 85.7% | | .344 |
| Beta-blocker | 58.6% | | 66.3% | | 66.1% | | 67.2% | | .163 |
| Aldosterone antagonist | 19.1% | | 25.1% | | 30.4% | | 42.4% | | <.001 |
| Diuretic | 64.8% | | 63.6% | | 71.7% | | 80.2% | | <.001 |
| Amiodarone† | 10.5% | | 13.7% | | 12.6% | | 13.8% | | .744 |
| Statins‡ | 34.5% | | 38.5% | | 36.8% | | 40.0% | | .711 |

ACE inhibitor/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; A-Fib, atrial fibrillation; BMI, body mass index; BP, blood pressure; LVEF, left ventricular ejection fraction; calcium × phosphate, calcium × phosphate product; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Data from 974 patients are reported as number (percentage) or median (interquartile range). Data for *NT-proBNP were available in 620, data for †amiodarone and ‡statins in 781 patients. For all other variables <5% of data was missing.

(n = 585, HR 1.64 [95% CI 1.30−2.07]; $P < .001$) and ≥65 years (n = 389, HR 1.44 [95% CI 1.12−1.84]; $P = .004$). In a sex-stratified multivariate model that included relevant clinical and laboratory predictors, a 1-mg/dL increase in baseline levels of serum phosphate was associated with a 26% (95% CI 1.04−1.52; $P < .001$) higher risk for death or heart transplantation (Fig. 1), even with adjustment for renal function. These results were further corroborated by regression splines that demonstrate an almost linear trend for higher event risk across serum phosphate values (Fig. 2).

In quartile-based sex-stratified analysis, individuals in the fourth quartile of serum phosphate were 2 times (HR 2.00 [95% CI 1.47−2.71]; $P < .001$) more likely to reach the endpoint as compared with the first quartile (Fig. 3). Respective HRs for the second quartile were 1.08 (95% CI 0.77−1.51; $P = .67$) and for the third quartile 1.18 (95% CI 0.84−1.64; $P = .34$). Corresponding 5-year cumulative transplant-free survival rates for ascending quartiles of serum phosphate were 69%, 68%, 67%, and 50%.

Formal testing for interaction between CKD status and phosphate levels with regard to the combined endpoint did not reveal statistical significance ($P = .23$). It therefore appears that CKD status does not modify the relationship between higher phosphate levels and poor outcome. In fact, the hazard for death or heart transplantation associated with higher phosphate levels was similar in individuals with (eGFR ≤ 60 mL − $min^{-1}$ × 1.73 $m^{-2}$, n = 277) (HR 1.61 [95% CI 1.26−2.06]; $P < .001$) and without (n = 652) (HR 1.35 [95% CI 1.08−1.69]; $P = .008$) CKD.

In contrast to phosphate, serum calcium levels were not related to the endpoint in the sex-adjusted univariate model (HR 1.17 [95% CI 0.97−1.41]; $P = .098$).

## Discussion

The present study demonstrates that serum phosphate even within the normal range is related to disease severity and the risk for adverse outcome in a large cohort of stable

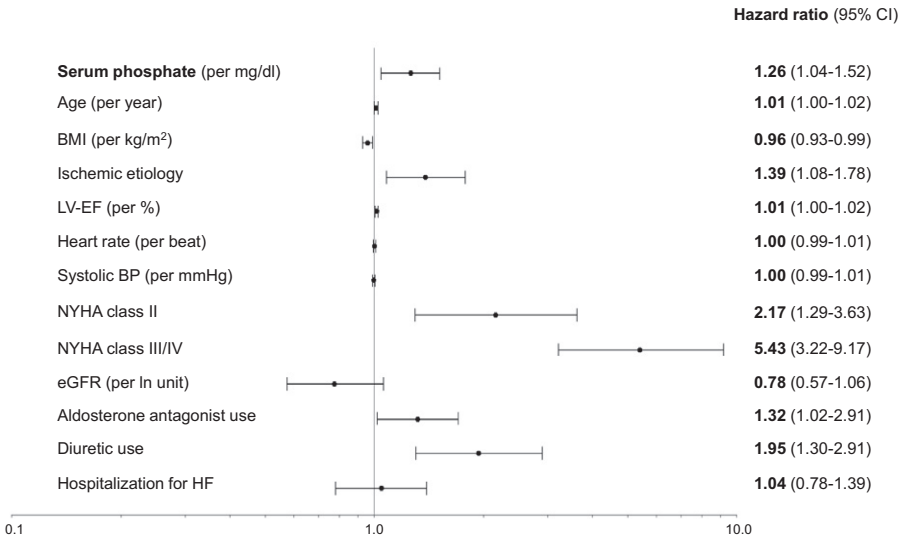


**Fig. 1.** Multivariate sex-stratified Cox regression analysis for death and heart transplantation. Hazard ratios and 95% confidence intervals are shown in a forest plot. BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

heart failure patients. This association is independent of concomitant CKD.

In clinical practice, elevated levels of serum phosphate usually reflect CKD. In end-stage renal disease, higher serum phosphate levels are associated with increased CVD mortality.[4,5] Recent publications have also shown a relation between serum phosphate and the risk for death and cardiovascular events in patients with prior MI.[6] Similarly, higher phosphate concentrations are related to increased CVD risk in individuals with no CKD or CVD.[7] Most recent data suggest that serum phosphate is associated with greater left ventricular mass cross-sectionally and with increased risk for heart failure prospectively in a large community-based sample of individuals without prior MI or CKD.[8]

In the present study, we found a graded, independent association between baseline phosphate levels and adverse

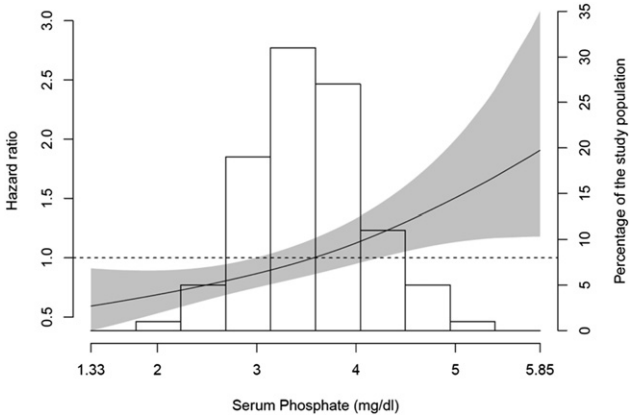


**Fig. 2.** Risk for all-cause death or heart transplantation by baseline levels of serum phosphate. The figure shows the hazard ratio (HR) for adverse outcome when serum phosphate was treated as a continuous variable by penalized spline regression. HR was adjusted for sex, age, body mass index, ischemic etiology, left ventricular ejection fraction, systolic blood pressure, New York Heart Association class, estimated glomerular filtration rate, and diuretic and aldosterone antagonist use. Line represents HR. Shaded area represents 95% CI for the HR. Bars represent the serum phosphate distribution.

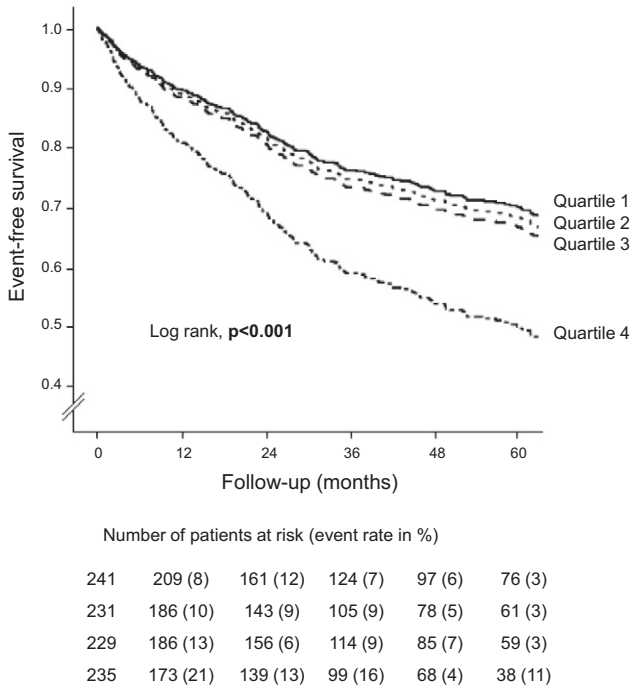


**Fig. 3.** Correlation between serum phosphate in quartiles and combined end point. Cumulative 5-year event rates were estimated by univariate, sex-stratified Cox proportional hazard regression analysis in 936 patients with congestive heart failure according to quartiles of serum phosphate levels at the study entry. Numbers of patients at risk and event rates are shown below the graphs.

clinical outcome in patients with stable heart failure. A 1-mg/dL increase in baseline levels of serum phosphate was associated with a 26% higher risk for death and heart transplantation. This association was independent of concomitant CKD and remained robust even in patients with serum phosphate within the normal range. Our results extend recent data that demonstrate an independent prognostic value of inorganic phosphate in a small cohort of stable heart failure patients.[18] In addition, in our study, serum phosphate was associated with severity of heart failure as measured by NYHA class, LVEF, and NT-proBNP levels.

These findings suggest that serum phosphate is of potential relevance not only in the pathogenesis of heart failure[8] but is also associated with disease severity and adverse outcome in patients with overt heart failure.

Although the retrospective nature of this cohort study does not permit inference of a causal relationship, there are several potential mechanisms that may explain the association of serum phosphate levels with heart failure progression.

Data from animal studies using 32P nuclear magnetic resonance spectroscopy suggest a substantial role for inorganic phosphate in cardiac energy metabolism and contractility. It has been hypothesized that inorganic phosphate is both the primary feedback signal for stimulating oxidative phosphorylation and also the most significant product of ATP hydrolysis in limiting the capacity of the heart to hydrolyse ATP.[19] Earlier it has been suggested that inorganic phosphate plays an important role in initiating the downregulation of myocardial contractile force at the onset of ischaemia.[20] Also, serum phosphate may directly promote vascular injury. Higher serum phosphate levels are associated with greater vascular smooth muscle cell calcification, especially when levels of calcium phosphate product are high, which may increase vascular stiffness and thus contribute to disease progression.[21,22] It has been reported that hyperphosphatemia stimulates an osteoblastic transcriptional program in the vasculature, which is mediated by osterix activation in cells of the vasculature tunica media and neointima.[23]

Besides these direct effects, phosphate may be indirectly involved in heart failure progression through its interactions with vitamin D, parathormone (PTH), and fibroblast growth factor 23 (FGF-23). For instance, elevated serum phosphate may be a marker of low vitamin D levels.[24] Low vitamin D is associated with potential promoters of heart failure progression such as greater plasma renin activity,[25,26] inflammation,[26] and higher blood pressure.[27] Low serum calcitriol concentrations are independently associated with poor clinical outcome in heart failure.[26,28,29] Higher serum phosphate has also been linked to secondary hyperparathyroidism, even in healthy individuals.[30] Higher levels of PTH have been shown to induce cardiac hypertrophy[10] and cytokine production,[31] both of which may contribute to disease progression. Recently, Schierbeck and coworkers reported an independent association between PTH with all cause and cardiovascular mortality in patients with stable heart failure.[29] Also, FGF-23, which is up-regulated by increased serum phosphate, has been linked to left ventricular hypertrophy and increased left ventricular mass in animal models,[32] in CKD patients,[33] and in an elderly community population.[34] Recently, FGF-23 has been shown to independently predict outcome in a small cohort of stable systolic heart failure patients.[18]

Finally, higher serum phosphate levels simply might reflect impaired renal function. Thus, severity of CKD rather than phosphate levels might account for the apparent association with adverse outcome. However, although estimation of eGFR based on serum creatinine, which was used in this study, has some limitations and data on proteinuria were not available, it appears less likely that our findings were confounded by the presence of renal insufficiency. The hazard for death or heart transplantation associated with higher phosphate levels was independent of eGFR and comparable in individuals with ($eGFR \leq 60\ mL \times min^{-1} \times 1.73\ m^{-2}$) and without CKD. In addition, no interaction was found between CKD status and the risk for death or heart transplantation associated with higher phosphate levels.

### Strengths and Limitations

We investigated a large cohort of well-defined patients with CHF using a longitudinal design with a long follow-up time and comprehensive adjustment for covariates at baseline. However, several limitations must be noted. No data on vitamin D levels, PTH or FGF-23 that regulates renal and intestinal phosphate absorption, and on phosphate intake were available, which could have helped to further delineate the underlying mechanisms for the association between serum phosphate and heart failure. Except for diuretics and mineralocorticoid receptor antagonists, we do not have data on other medication that might have influenced serum phosphate levels. Finally, a further limitation arises from the fact that data derive from a single-center study. Therefore, the results need to be confirmed elsewhere.

## Summary

We found a graded, independent relation between serum phosphate levels even within the normal range, disease severity, and adverse outcome in patients with chronic heart failure. The excess risk for death or heart transplantation was present in patients with and without evidence of kidney disease. These results further highlight the role of serum phosphate not only in CKD and coronary artery disease but also in CHF. Additional research is warranted to confirm our results and to elucidate the underlying mechanisms.

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## Disclosures

None.

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