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EDITORIAL COMMENT

Fibroblast Growth Factor-23 Fans the Flames of Heart and Kidney Failure*

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Chronic kidney disease (CKD) promotes cardiac injury, and heart failure begets kidney injury. Although shared risk factors such as diabetes, hypertension, and atherosclerosis are well-known igniters of the combustible interaction between chronic heart and kidney diseases, identification of the accelerants that drive the full-fledged public health conflagration of "cardiorenal" disease is a hot area of investigation.

At the nexus of heart and kidney diseases, elevated levels of the bone-derived, phosphate-regulating hormone fibroblast growth factor (FGF)-23 has emerged as a novel candidate accelerant. FGF-23 levels increase early in the course of CKD and are strongly predictive of cardiovascular events and death, independently of traditional and CKD-specific risk factors (1,2). As a putative underlying molecular mechanism, laboratory data suggest that elevated FGF-23 can injure cardiac myocytes through a novel α-Klotho–independent pathway that results in left ventricular hypertrophy (3). Reflecting the bidirectional role of FGF-23 in cardiovascular and kidney diseases, pre-existing heart disease is now increasingly recognized as another leading cause of chronically elevated FGF-23. Although it is currently unknown if subclinical CKD underlies elevated FGF-23 levels in heart disease or whether heart disease itself increases FGF-23 independently of kidney dysfunction, several studies demonstrated that higher FGF-23 levels predict an increased risk of cardiovascular events in patients with pre-existing heart disease (4,5).

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In this issue of *JACC: Heart Failure*, Wohlfahrt et al. (6) venture into this dynamic area by conducting a prospective cohort study of 369 individuals with established and severe systolic heart failure who were enrolled on admission for consideration of heart transplantation or placement of a ventricular assist device, biventricular pacemaker, or implantable cardioverter-defibrillator. During a median follow-up of 536 days, higher baseline FGF-23 levels were independently associated with an increased risk of the development of the composite outcome of urgent heart transplantation, implantation of a ventricular assist device, or all-cause mortality. Although limited power likely necessitated use of the composite outcome, it would have been particularly important to confirm that FGF-23 was associated with the "hard" outcome of mortality given that the composite endpoint included placement of a ventricular assist device, the consideration of which was also a reason for entry into the cohort. Nonetheless, assuming that elevated FGF-23 is indeed an independent risk factor for cardiovascular events in advanced heart failure, we now have solid outcomes data linking higher FGF-23 levels to an increased risk of cardiovascular events spanning the general population, early and advanced CKD, and the coronary artery disease and heart failure populations (7).

Although it is impossible to pinpoint precise mechanisms that may underlie the association of FGF-23 with cardiovascular events in the current observational study, we can speculate several possibilities.

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Perhaps elevated FGF-23 directly exacerbated cardiac myocyte dysfunction. Perhaps higher FGF-23 reflected greater ectopic FGF-23 expression by more severely diseased hearts, as suggested by preliminary animal data (8). Perhaps the effects of elevated FGF-23 were mediated by the concomitant deficiency of α-Klotho, which serves as the coreceptor for FGF-23 in the kidney. Reflecting their interrelationship, FGF-23 levels are markedly elevated in genetic models of α-Klotho deficiency, whereas primary overexpression of FGF-23 in transgenic mice induces α-Klotho deficiency (3,9). The extent to which the strong association between elevated FGF-23 and clinical outcomes are mediated by α-Klotho deficiency versus FGF-23 excess or both is currently debated. Laboratory studies offer evidence of direct toxicity of each, but previous human studies that compared the 2 demonstrated significant effects only for FGF-23 (10). Likewise, Wohlfahrt et al. (6) report no association between serum levels of the soluble form of α-Klotho with FGF-23 levels or clinical outcomes. Whether this reflects shortcomings of the current α-Klotho assay or an accurate indictment of FGF-23 over α-Klotho requires further study.

On the basis of previous studies that reported stronger associations between elevated FGF-23 and cardiovascular events in their CKD versus non-CKD subgroups (11,12), underlying CKD would be considered a likely link between elevated FGF-23 and cardiovascular events in the current study. However, in an unexpected finding, stratified analyses by the absence or presence of CKD, defined as an estimated glomerular filtration rate (eGFR) $<$60 ml/min/1.73 m^2, demonstrated that FGF-23 was independently associated with adverse outcomes only in the non-CKD stratum. The current study's unique population may account for this apparent divergence from previous findings. By focusing exclusively on nearly end-stage heart failure patients, the authors enrolled a more homogeneous and sick population than previous FGF-23 studies, and it is possible that the eGFR underestimated the true prevalence of kidney dysfunction. In this setting, elevated FGF-23 could have served as a discriminating biomarker of subclinical CKD. Interestingly, the median FGF-23 of 148 relative units (RU)/ml (interquartile range [IQR]: 86 to 359 RU/ml) in the current cohort was virtually identical to the median of 145 RU/ml (IQR: 96 to 239 RU/ml) in the Chronic Renal Insufficiency Cohort Study of individuals with moderate to severe CKD (13). Even among the 63% of individuals identified as not having CKD in the current study, the median level of FGF-23 of 120 RU/ml (IQR: 73 to 263 RU/ml) was consistent with levels observed in moderate CKD. If the study population actually included a substantial number of individuals with kidney dysfunction but relatively preserved eGFR who were correctly identified by elevated FGF-23, this could explain why a higher FGF-23 level was predictive of poor outcomes in the "non-CKD" stratum but not in the participants whose CKD was already clearly conveyed by reduced eGFR. In other words, the main results reported in the non-CKD stratum, paradoxically, may have been driven by occult CKD.

On the basis of their finding that treatment with angiotensin-converting enzyme (ACE) inhibitors significantly attenuated the risk of reaching the composite endpoint only among individuals with FGF-23 levels ≥200 RU/ml, the authors propose that FGF-23 could serve as a novel biomarker to help clinicians identify heart failure candidates for ACE inhibitor therapy. However, several factors justify caution in drawing therapeutic conclusions from these observational data. Because ACE inhibitors are a first-line treatment for systolic heart failure, most, if not all, patients should have been undergoing treatment when it was ascertained at study entry. Those who were untreated were likely fundamentally different from those who were and in ways that would plausibly influence outcomes. For example, the untreated group could have included patients in whom ACE inhibitor therapy previously failed because of worsening kidney function or patients who were receiving globally inferior quality of care. In either case, the absence of ACE inhibitor therapy would have selected individuals at higher risk of cardiovascular events. Using propensity score matching on the likelihood of receiving ACE inhibitors would have mitigated this form of bias, but only randomization could eliminate it. Interestingly, in a secondary analysis of a clinical trial of ACE inhibitors in stable coronary artery disease, treatment was most effective in patients with the highest FGF-23 levels (14). Although these results support the authors' conclusion to use ACE inhibitors in patients with high FGF-23 levels, because systolic heart failure itself is a proven indication for ACE inhibitor therapy (15), it is unclear how FGF-23 testing would alter heart failure management.

Nevertheless, the current study highlights the potential of FGF-23 as a novel risk factor for cardiovascular events in severe systolic heart failure. Further studies are needed to characterize FGF-23 levels and test their association with outcomes across the spectrum of heart failure severity and to disentangle the extent to which heart failure raises FGF-23 levels independently of frequently coexisting kidney dysfunction. If elevated FGF-23 is found to be a causal mechanism of cardiovascular events, targeting FGF-23

excess could represent a novel approach to extinguish the flammable blend of heart and kidney failure.

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