Clinical vignette: A 48-year-old man with chronic kidney disease stage five due to type II diabetes mellitus and hypertension was referred for hemo-
dialysis initiation. His physical exam showed a blood pressure of 150/80,
normal fundi, a positive fourth heart sound (S4), and trace pedal edema. 
Moderate aortic calcification was present on prior chest X-ray. The ECG 
showed left ventricle hypertrophy by voltage and slight prolongation of 
the QT interval. Medications included chlorthalidone, amlodipine, carve-
dilol, cholecalciferol, erythropoietin, and a phosphate binder. What ad-
ditional therapy should be initiated to reduce vascular calcifications and 
cardiovascular mortality?

Current therapy
Cardiovascular disease (CV) is a major cause of morbidity and mortality in patients with 
chronic kidney disease (CKD), especially in those with end-stage renal disease (ESRD) 
undergoing thrice weekly hemodialysis (1). Indeed, the risk of CV-related mortality is 10- 
to 20-fold higher in hemodialysis patients. Interestingly, unlike the general 
population, in which coronary atherosclerotic disease is the principal cause of CV 
mortality, patients with CKD expire from chronic heart failure and sudden cardiac 
events. This is consistent with the fact that left ventricular hypertrophy (LVH) and vas-
cular calcification are the most apparent cardiovascular abnormalities in patients 
with CKD (2). Many therapeutic strategies have failed to improve LVH, vascular calcifi-
cations, or survival in large-scale randomized 
controlled trials (RCTs) of patients with 
ESRD. Treatment with erythropoietin and statins and manipulation of hemodi-
yalysis prescription do not appear to lower 
lower mortality in ESRD (3, 4), nor do thera-
peutic strategies that address the mineral 
imbalance associated with CKD impact on 
CV, including vitamin D therapy (PRIMO 
study), calcimimetics (EVOLVE study), 
phosphate binders, and calcium-free phos-
phate binders (4–6). Small RCTs evaluating 
angiotensin receptor blockers (7) and the 
nonselective β/α1-blocker carvedilol (8) 
suggest that these agents may reduce car-
diovascular mortality in CKD, but these 
conclusions need to be substantiated in 
larger clinical trials. Nevertheless, activa-
tion of the renin-angiotensin-aldosterone 
system (RAAS) may contribute to LVH and 
myocardial fibrosis in CKD. It is unclear 
how RAAS is activated in CKD.

Knowledge gap
Simplistically, hypertension and increased 
arterial stiffness of calcified arteries should 
lead to LVH; however, the pathogenesis of 
LVH and vascular calcifications and their 
relationship to mineral metabolism per-
turbations are proving to be complex and 
refractory to current treatment strategies. 
A new idea is that chronic elevation of the 
bone-derived hormone FGF23 is associated 
with LVH and vascular calcifications and their 
relationship to mineral metabolism per-
turbations is controversial because 
α-Klotho coreceptors in

Conflict of interest: The author is a consultant for 
Ammgen and Cytochroma and participates in the Amgen-

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Research advances
In this issue of the JCI, Voelkl and colleagues 
link elevated aldosterone levels with vascular 
calcification and provide a mechanism for RAAS activation and subsequent LVH in 
CKD (14). They report that, in klotho-hypo-
morphic (kl/kl) mice, aldosterone directly 
stimulates vascular calcification by induc-
ing P1T1-dependent phosphate transport in 
vascular smooth muscle cells via direct 
activation of the mineralocorticoid receptor. 
Importantly, the mineralocorticoid receptor 
antagonist spironolactone reduced vascular 
and soft tissue calcification and increased 
the life span in this model of α-Klotho 
deficiency. These findings are consistent 
with several prior animal studies showing 
that aldosterone blockade affords vascular 
protection and reduces vascular calcifica-
tions through blood pressure-independent 
mechanisms (15–17).

Vascular calcifications are known to be 
associated with increased mortality, pre-
sumably through development of LVH in 
CKD; consequently, elevations of aldoster-
one in a α-Klotho–deficient CKD model 
may also promote vascular calcification. 
These conclusions should be extrapolated 
to human CKD with some reservation.

Reducing cardiovascular mortality in chronic kidney disease: something borrowed, something new

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The attending physician
First, kl/kl mice are a model of primary loss of α-Klotho, and consequent elevations in FGF23 and 1,25(OH)₂D, which likely arise from end-organ resistance to FGF23, lead to severe hyperphosphatemia and hypercalcemia. In contrast, reductions in α-Klotho in CKD are likely secondary to excess FGF23 and decreased 1,25(OH)₂D, both of which are known to suppress α-Klotho expression in the kidney. Thus, the abnormalities of mineral metabolism and the mechanism of increased aldosterone may differ between kl/kl mice and models of CKD. Nevertheless, these and other studies reporting that aldosterone targets vascular smooth muscle cells to stimulate vascular calcifications (15–17) suggest that aldosterone is the proximate mediator of cardiovascular and vascular toxicity in CKD.

**Recommendations**

Mineralocorticoid receptor antagonists are standard medical therapy for patients with moderate to severe heart failure symptoms and reduced left ventricular ejection fraction and for patients with heart failure after myocardial infarction in the general population. In addition, activation of the RAAS is profibrotic, whereas inhibition of this pathway is antifibrotic for the myocardium. Therefore, should we borrow this treatment for use in ESRD to treat LVH, hypertension, and vascular calcifications? Although hyperkalemia is a concerning complication of aldosterone antagonism in the setting of CKD, studies of chronic heart failure in patients with ESRD indicate that these agents may be used with close monitoring of serum potassium levels (18–21). The long-term outcomes of combined use of ACEI, angiotensin receptor blockers, and mineralocorticoid receptor antagonists in patients with ESRD have not been evaluated in rigorous, well-designed RCTs, thus the benefits and adverse consequences of single and combination therapies in this setting are unknown. The data supporting actions of both Ang II and aldosterone to stimulate cardiac and arterial blood vessel remodeling suggest that such trials may be warranted in ESRD (22).

Should we also consider new therapies to inhibit FGF23 to reduce LVH? Before recommending such therapy it will be necessary to confirm that FGF23 directly or indirectly stimulates myocyte growth leading to LVH in CKD. It will also be important to determine at what point during the course of progressive CKD that adaptive compensatory elevations of FGF23 become maladaptive. For example, treatment of animal models of CKD with neutralizing FGF23 antibodies increased rather than decreased mortality (23). Finally, the optimal range of serum FGF23 levels needs to be determined.

There are potential strategies to reduce FGF23 in CKD. In addition to blocking antibodies, FGFR inhibitors, which are being developed as cancer therapeutics, inhibit both the production (24) and end-organ effects of FGF23 (25). Serum FGF23 concentrations can also be reduced in ESRD by treatment with cinacalcet in combination with low-dose vitamin D analogues (26). Future trials are needed to explore multifaceted interventions geared toward improving survival by targeting the proximate pathophysiological factors responsible for increased cardiovascular mortality in CKD.

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