In patients with CKD renal excretion of dietary phosphate, which is consumed in the form of protein and phosphate additives, becomes increasingly difficult as nephron mass decreases. Potent compensatory mechanisms — mainly driven by PTH and FGF-23 — can prevent the occurrence of hyperphosphatemia until late in the course of the disease as it progresses towards renal failure.4,5 Whether the maintenance of normal serum phosphate levels in CKD indicates protection against tissue phosphate accumulation is a matter of debate. Phosphate excess could have direct or indirect adverse effects.1,3,6 Hyperphosphatemia, and even increases in serum phosphate levels within the normal range, are associated with worse cardiovascular and global outcomes.5 Although hyperphosphatemia can be partially or fully corrected using phosphate binders, whether such correction results in improved patient outcomes remains unclear.7

Phosphate and bone
Bone is the main phosphate reservoir in the body; non-osseous soft tissues contain <20% of total body phosphate. If bone resorption outweighs bone formation, net loss of phosphate and calcium occurs.1,2 PTH is a key regulator of bone resorption and turnover. High PTH levels stimulate both bone formation (either directly or indirectly by suppressing the osteogenic expression of sclerostin) and resorption (by increasing osteocytic expression of RANKL).1,2,3,4,5 Persistent elevations of PTH favour bone resorption over formation, whereas intermittent elevations suppress the osteocytic expression of sclerostin (and thus RANKL) and increase bone formation.1,2,3,4,5 Many factors modulate FGF-23 synthesis in osteocytes, phosphate, calcium, PTH, 1,25(OH)2D3 and its analogues, leptin, osteotropins, soluble Klotho, hormonal autocrine and paracrine loops in bone and osteocytes.2,3,4,5 In osteocytes, FGF-23 and PTH stimulate synthesis of 1,25(OH)2D3, which at higher calcemic levels inhibits NaPi-2a and NaPi-2c. The majority of FGF-23 circulates, whereas phosphatase and serum phosphate levels in the setting of osteitis fibrosa or adynamic bone disease stimulate calcification of soft tissues, including the vasculature.6

Renal phosphate handling and retention
Following ultrafiltration of plasma phosphate in the glomerulus, the majority is reabsorbed in the proximal tubule via NaPi-2a and NaPi-2c on the luminal side and an unknown transporter on the basolateral side of tubular epithelial cells. In the steady state FGF-23 and PTH maintain phosphate homeostasis by adapting renal phosphate handling and urinary excretion to oral intake. Binding of FGF-23 and PTH to their respective receptors on tubular epithelial cells activates signaling pathways that inhibit NaPi-2a and NaPi-2c. The renal action of FGF-23 requires a Klotho, which can also directly inhibit NaPi-2a and NaPi-2c. FGF-23 inhibits and PTH stimulates synthesis of 1,25(OH)2D3 in the tubular epithelium. In the absence of CKD, phosphate retention as a result of reduced NaPi-2a and NaPi-2c expression is presented by increases in serum FGF-23 and PTH.1,2 As CKD progresses a Klotho expression is reduced, which results in increased FGF-23 resistance. Increased concentrations of FGF-23 are therefore required to maintain phosphate excretion. In late-stage CKD, these adaptive mechanisms become insufficient and hyperphosphatemia ensues.

Vascular calcification
High serum FGF-23 and reduced α-Klotho levels in association with hyperphosphatemia increase the risk of cardiac dysfunction, cardiovascular events and cardiovascular mortality in patients with CKD.1,3 Circulating PTH, FGF-23 and α-Klotho independently exert direct, acute actions on the structure and function of arterial endothelial cells, smooth muscle cells and cardiomyocytes. Chronic FGF-23 excess promotes left ventricular hypertrophy by a direct, α-Klotho-independent action on cardiac muscle that involves binding to FGFFR4 and activation of the PLC/Pi3K/Akt/mTOR pathway.2 By contrast, α-Klotho protects against aortic tissue-inositol-trisphosphate vascular endothelial cell dysfunction and left ventricular hypertrophy through inhibition of oxidative stress and the p38 and ERK1/2 signalling pathway.2

Cardiovascular dysfunction
Although 70% to 90% of ingested phosphate is absorbed by the gut, active phosphate transport is stimulated by 1,25(OH)2D3 and involves NaPi-2b on the luminal side and a Na/2H+ exchanger on the basolateral side of enterocytes; passive transport occurs by diffusion via the intercellular space.2,3 Phosphate binders reduce intestinal phosphate absorption, inhibitors of active phosphate transport, such as tetracaine, nicoretine and nicotinic acid are not currently used in the clinic.2,3

Competing interests
T.B.D. has received speaker fees and honoraria from Amgen, F Hoffmann-La Roche, Fresenius Medical Care, Kyowa Hakko Kirin, Janssen-Cilag, and Pfizer. T.B.D. has received non-monetary support (e.g., research funding) from Amgen, F Hoffmann-La Roche, and Fresenius Medical Care. T.B.D. has served as a member of the steering committee for a randomized feasibility trial from Amgen, Sarah, and Shire. Edited by Elise E. Carney, designed by Joanne C. Rouse. Copyright © 2015 Nature Publishing Group. All rights reserved. For permission to use, contact naturepermissions@nature.com.