Phosphate levels are consistently linked with cardiac calcification, cardiovascular disease (CVD), and death in populations with chronic kidney disease. In addition, mechanistic insights suggest that phosphate levels that span the conventional normal range could lead to CVD. Examining these associations in the general population may be relevant because several interventions that may be suitable for primary or secondary prevention trials already exist. This review summarizes findings described from several community-based, prospective, observational studies. Graded associations with cardiac calcification, left ventricular hypertrophy, cardiovascular events, and death were evident, and cardiovascular risk seemed to accelerate with phosphate >3.5 to 4.0 mg/dl. Although the cause of these associations remains to be determined, several existing interventions may allow in-depth examination of the hypothesis that reducing phosphate levels could prevent CVD in the general population. Even as proof-of-concept trials and mechanistic studies are awaited, phosphate levels may be useful for cardiovascular risk stratification in adults without overt kidney disease.

"Metastatic calcification" has an impressively long provenance, dating back to a publication by Virchow in 1855 titled “Kalkmetastasen” (“Chalk Metastases”) (1). The association between radiologic vascular calcification and uremia has been known for several decades (2). A notable study from the 1970s reported autopsy findings from 57 patients who had and 18 patients who had not undergone dialysis and had chronic uremia: Pathologic features were predominantly present in the medial layer of coronary arteries, and atheroma was not a dominant feature (3). Research into the vascular calcification of uremia accelerated around the beginning of this millennium, possibly because of epidemiologic studies linking calcium, phosphate, and mortality in dialysis populations; advances in imaging technologies that quantify vascular calcification; general population studies linking vascular calcification to cardiovascular outcomes; and the advent of newer pharmaceutical products for treating metabolic bone disorders. Unfortunately, detailed review of all of these is beyond the purview of this article.

Before this surge of research activity, there seemed to be an inverse relationship between the enthusiasm of the nephrology community for the hypothesis that hyperphosphatemia causes large-vessel dysfunction in advanced chronic kidney disease (CKD) and the body of supportive evidence. Although supportive evidence has been slow to accumulate, several observational studies in populations with CKD emerged to suggest a role for phosphate in vascular calcification of smaller arterial beds, most especially the coronary arteries (4–12). In this regard, the observation that cardiac calcification developed quickly in young adults after inception of maintenance dialysis generated particular alarm and probably stimulated research activity (12). Advances in imaging technologies have been pivotal in creating awareness about vascular calcification in humans; however, imaging technologies, to date, do not allow us to determine whether a given calcific focus comes from vascular intimal or medial layers. Although most physicians, especially nephrologists, have traditionally believed that intimal and vascular calcification have very different causes and effects (13), it has also been hypothesized that both entities are manifestations of a single pathophysiologic process (14). Basic research into uremic vascular calcification has also accelerated and several lines of evidence directly challenge the dictum that vascular calcification is an entirely passive, concentration-dependent precipitation phenomenon with few pathophysiologic consequences. Without wishing to burden the reader with a comprehensive review of this burgeoning literature, several insights are worth highlighting (15). One key finding was the ability for vascular smooth muscle cells to transform into cells with chondrocyte-like or osteoblast-like phenotypes, especially in the presence of CKD, aging, diabetes, and inflammation, with downstream consequences including local production of collagen and noncollagenous proteins in intimal and medial layers, incorporation of calcium and phosphorus into matrix vesicles, and vascular mineralization. Although several inhibitors of calcification are known, both circulating (e.g., fetuin A) and locally active (e.g., matrix Gla protein, osteopontin, pyrophosphate), it is becoming evident that phosphorus levels, per se, are important in the process of vascular calcification. For example, Mathew et al. (16) recently reported findings from a study of vascular smooth muscle cells derived from atheroscle-
rotic human aortas. Of note, matrix mineralization was primarily related to ambient phosphorous concentrations. In addition, among atheroma-prone uremic mice, hyperphosphatemia led to aortic mineralization and oral phosphate binders prevented mineralization. High phosphate levels may also promote cardiovascular disease (CVD) through mechanisms other than vascular calcification. For example, inactivation of Klotho or fibroblast growth factor 23 in mice leads to CVD, and it has been hypothesized that extracellular phosphate modulates ambient levels of several circulating factors that could lead to CVD, such as Klotho, phosphatonin such as fibroblast growth factor 23, and parathyroid hormone and calcitriol (17).

Several epidemiologic studies examined associations between cardiovascular events and serum calcium, phosphorus, calcium-phosphorus product, and parathyroid hormone in dialysis populations (18–21). Associations between hyperphosphatemia and cardiovascular outcomes and death that persisted when adjustment was made for comorbidity and commonly measured care-related biomarkers were seen in all of these studies. Studies at ever-earlier stages of CKD have begun to materialize; findings mirror those seen in ESRD, and phosphate levels have been linked with more rapid progression of CKD, cardiac calcification, CVD, and death (22–24). Although associations between phosphate and adverse outcomes in patients with CKD persisted when adjustment was made for estimated GFR, it is probably fair to say that concerns that high phosphate levels reflect declining GFR have not been fully allayed by these studies. In particular, these studies have generally estimated GFR from serum creatinine. It is plausible that declining GFR, in combination with declining muscle mass, could lead to rising phosphate levels and enhanced risks for CVD, renal replacement therapy, and death, without affecting serum creatinine levels. In this scenario, artifactual associations between phosphate and adverse events would be expected, even with adjustment for creatinine-based GFR estimates. This being said, observations from populations with CKD are pertinent because they suggest that phosphate-associated risk may start at far lower phosphate levels than previously believed.

There is no obvious reason for why advanced kidney disease should be a prerequisite for calcium-phosphate abnormalities to cause CVD. If high phosphate levels cause vascular disease in patients with CKD, then it seems logical to hypothesize that a similar relationship exists among individuals with normal or near-normal kidney function. Because therapeutic research targeting these abnormalities has advanced rapidly in CKD, finding such associations might have implications for risk stratification, treatment, and future research directions in the overall population. The Framingham Offspring Study was the first community-based examination of the association between normal-range phosphate levels and CVD (25). This cohort had a mean age of 44 yr at study inception, and follow-up extended to 16 yr. Even when adjustment was made for GFR, urinary protein excretion, C-reactive protein, and traditional cardiovascular risk factors, phosphate levels were associated with incident CVD, to the extent that participants with levels ≥3.5 mg/dl had hazards ratios 1.55 times higher than those with values ≥2.8 mg/dl.

We also tested the hypothesis that phosphate level may be a cardiovascular risk factor in the Atherosclerosis Risk in Communities Study (ARIC), in which 15,732 adults were followed prospectively for almost 13 yr (26). Generalizability is an attractive feature of this ongoing study, because probability-based sampling methods were used. A total of 27.1% of participants were black, and average age was 54 yr. Mean calcium, phosphate, and creatinine-based GFR values were 10.3 mg/dl, 3.4 mg/dl, and 93.1 ml/min per 1.73 m², respectively. We tested a large battery of candidate variables for their association with baseline phosphate levels, and several expected associations were confirmed (the presence of previous CVD, plaque on carotid ultrasound testing, older age, lower GFR, and higher dietary phosphorus intake). Several other associations, however, were also evident. For example, associations with individual components of the metabolic syndrome were inconsistent in direction, because phosphate was associated higher LDL, HDL, and triglyceride levels and lower body mass index, fasting glucose, and BP levels. Perhaps the most striking overall finding was the observation that a mere 15% of phosphate variance could be explained in this well-characterized population. Although accounting for the “missing” 85% clearly throws down the gauntlet for future research, it is tempting to speculate about the contribution of genetic and epigenetic factors. With regard to cardiovascular events during the follow-up period, baseline phosphate levels were associated with future occurrences of stroke and death but not with coronary heart disease. The ARIC report has obvious limitations, and experimental studies are clearly needed before causation can be determined or treatment recommendations can be made. From the perspective of an observational study, some highly desirable data elements were not available, including vitamin D, parathyroid hormone, isotopic GFR, urinary protein excretion, inflammatory markers, adipokines, and genetic profiles.

Coronary artery calcification (CAC) is believed to be an accurate surrogate of atheroma burden, and examining relationships between phosphate and CAC could help to clarify mechanisms that link phosphate levels and CVD. We recently examined these relationships in the Coronary Artery Risk Development in Young Adults (CARDIA) study, an ongoing, prospective study of CVD in adults aged 18 to 30 in four metropolitan areas of the United States (27). Like ARIC, the generalizability of CARDIA is probably robust, because random sampling methods were used to generate population-based samples balanced by age, gender, race, and schooling. At baseline, mean phosphate level and estimated GFR levels were 3.6 mg/dl and 116.6 ml/min per 1.73 m², respectively. Like ARIC, associations of serum phosphate were multifaceted (including younger age, female gender, black race, smoking, family history of myocardial infarction, lower body mass index, HDL cholesterol, triglycerides, lower systolic BP, diastolic BP, exercise intensity score, lower carbohydrate intake, and use of cardiac medications), and, also like ARIC, explained variance was low, at 9%. CAC was present in 9.6% of the study population after 15 yr of follow-up. Possibly reflecting the complexity of its baseline correlates, associations between baseline phosphate levels and CAC were highly dependent on covariate
adjustment; when no covariate adjustment was attempted, higher phosphate levels were associated with a lower likelihood of CAC; in contrast, higher phosphate levels were associated with a greater likelihood of CAC in models that accounted for classic cardiovascular risk factors, and P-spline analysis suggested a threshold phosphorus level of 3.9 mg/dl for CAC. That study exhibited all of the limitations of the previously described study with the ARIC database; in addition, CAC was not measured sequentially, and it could not be determined for certain whether high phosphate levels preceded CAC or vice versa.

Predating the comparatively recent phosphate–atherosclerosis debate, it was widely conjectured that the cardiovascular effects of high phosphate levels in ESRD were through maladaptive remodeling of large blood vessels. Although large-vessel remodeling is difficult to quantify at a clinical level, left ventricular size and morphology are widely accepted surrogates. If normal-range phosphate levels lead to abnormal vascular remodeling in community-dwelling adults, then left ventricular enlargement should be expected to follow. The CARDIA study also facilitated an attempt at addressing this hypothesis, albeit indirectly, by relating baseline phosphate levels to echocardiographic findings 5 yr later (28). Defined as mass index >131 g/m² in men and >100 g/m² in women, left ventricular hypertrophy was associated with higher phosphate levels 5 yr previously, regardless of whether covariate adjustment was used. P-spline analyses suggested that the risk for left ventricular hypertrophy became evident with phosphate levels above thresholds of 3.5 to 4.0 mg/dl. As with CAC findings in CARDIA, our study did not assess left ventricular mass index sequentially, and the temporal sequence linking phosphate to left ventricular hypertrophy is unclear.

Another representative, community-based study (Multi-Ethnic Study of Atherosclerosis) quantified cross-sectional associations between phosphate levels and ankle-brachial index, pulse pressure, and arterial elasticity profiles. As in previously described community-based studies and mirroring findings in the US population in general (29), the association between phosphate and traditional cardiovascular risk factors was distinctly heterogeneous. With regard to vascular correlates, phosphate levels >4 mg/dl were associated with ankle-brachial index, even with covariate adjustment. For pulse pressure and arterial rigidity, unadjusted associations with high phosphate levels disappeared when traditional cardiovascular risk factors were taken into account (30).

Findings from the five community-based studies described here are broadly consistent with those from observational studies in populations with ESRD, CKD, and overt CVD (31). Although these studies suggest that phosphate reduction strategies may reduce CVD in the general population, it may we worth pointing out that, to date, even consistent findings from observational studies in CKD have never been confirmed in large, randomized trials with “hard” outcomes. Determining the mechanisms linking phosphate levels to general-population CVD, whether direct or through currently unknown confounders, may be an exciting avenue of future research. With regard to intervention trials in patients without overt kidney disease, the responsiveness of serum phosphate levels to preexisting treatments might be an obvious next step. If such treatments are identified, then primary and secondary prevention trials may be indicated to assess the effect of interventions that combine simplicity, cheapness, lack of toxicity, and phosphate-reducing capacity. Although the wait for these studies may be long, it seems already apparent that, regardless of mechanism, knowing phosphate levels may help with risk assessment in the general population, just like they do in patients with CKD.

Disclosures
R.N.F. has received consulting fees from Abbott, Genzyme, and Amgen.

References


