What Can We Learn from Null Randomized Controlled Trials?

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doi: 10.1681/ASN.2013030295

Cardiovascular disease is an important cause of mortality and morbidity in patients with CKD. Elevated serum phosphorus concentration is associated with an increased cardiovascular event rate. Recent data suggest that even in the normal range, serum phosphorus concentration is associated with an increased cardiovascular event rate.1 The mechanism of this association remains unclear. This issue of JASN contains a report of a randomized controlled trial by Chue et al. regarding the cardiovascular effects of sevelamer in stage 3 CKD.2 Before I discuss the trial, I congratulate the investigators for adding another randomized trial to the meager number of trials in nephrology. Their well-conducted trial and transparent reporting are evident in their study. The editors also need to be congratulated for having the courage to publish a null trial in a prestigious journal.

Chue et al. hypothesize that phosphorus concentration, even within the normal range, by increasing the plasma level of fibroblast growth factor 23 (FGF-23), would provoke left ventricular hypertrophy, diastolic dysfunction, and systolic heart failure, finally culminating in increased cardiovascular morbidity.2 Accordingly, they designed a single-center, double-blind, placebo-controlled, randomized trial to test the hypothesis that the noncalcium-containing phosphorus binder, sevelamer, would reduce gut phosphorus absorption, reduce FGF-23, reduce left ventricular mass and arterial stiffness, and improve systolic and diastolic cardiac performance.

After a 4-week run-in with open-label sevelamer, in which 120 participants with stage 3 CKD were given 1600 mg of sevelamer with each meal, the authors then randomized 55 participants to the active drug, sevelamer, and 54 participants to placebo. During the run-in period, 8% of the patients became hypophosphatemic and had to drop out. Over the subsequent 36 weeks, the patients adhered to this regimen; as may be expected, about 56% of the patients took >80% of their prescribed medication. Medication adherence was similar between the sevelamer and placebo groups.

Several characteristics at baseline are noteworthy. Serum phosphorus concentration was not elevated before randomization; at baseline, the phosphorus concentration was 3.16 mg/dl. This was an a priori decision because higher serum phosphorus even within the normal range is associated with increased cardiovascular mortality.1 Thus, the hypothesis tested in this trial was based on epidemiologic observations alone. Furthermore, the parathyroid hormone (PTH) was not elevated, and both the median albumin/creatinine ratio and median BP that were near normal also improved. Because there was no placebo in the open-label run-in, it is unclear whether these effects are because of observation or because of drug. It is likely that this is a study effect, simply due to change in habits of participants due to observation.

Somewhat contrary to expectation, there were no effects of the drug on lowering of serum phosphorus concentration, or reduction in the urinary excretion of phosphorus, PTH, and 1,25-dihydroxy vitamin D levels. Thus, there was little effect on mineral metabolism provided by the sevelamer therapy over the 36 weeks of the trial. Even among participants who took >80% of the prescribed treatment, both phosphorus concentration and vitamin D levels remained unchanged. In the adherent subgroup, the only change observed was the reduction in urinary phosphorus concentration and FGF-23. Therefore, in large measure, the drug was unable to affect mineral metabolism in the participants. One has to ask whether the drug is ineffective. However, this is unlikely to be the case because the drug is certainly approved with adequate trial data to support its use in people with hyperphosphatemia. In this trial, the drug in the doses used was not effective in reducing an already normal level of phosphorus concentration. Perhaps the participants increased the dietary phosphorus intake and therefore an overall decline in serum phosphorus concentration was not seen. In fact, there is some evidence that sevelamer reduced serum phosphorus concentrations; in four patients receiving the drug, hypophosphatemia was observed and three patients had to be excluded from further participation in the trial. Interestingly, three participants in the placebo drug group also developed hypophosphatemia, only one of which had to be excluded.

Unsurprisingly, at the end of the trial, no differences were seen in cardiac structure or function as assessed by cardiac magnetic resonance imaging (MRI) or echocardiography. In addition, ambulatory BP and pulse wave velocity, a measure of arterial stiffness, remained unchanged.

This trial was unable to reject the null hypothesis and it adds to the growing list of null trials in nephrology. The first question one has to answer is whether the trial was adequately powered. In the past, at least one trial of even a smaller sample size was able to show between-group improvement in left ventricular mass over a similar duration of the study.3 However, before we conclude that the study was adequately powered, we need to address the second question of whether a
reduction in dietary phosphorus absorption can improve cardiovascular structure and function. From the results of the study of Chue et al., the answer appears to be no—at least, not a large improvement for the patients studied. By examining the inclusion criteria for this study we can glean that participants who were taking any binder for the prior year were excluded. Participants who had hyperparathyroidism or had an abnormal serum phosphorus concentration were also excluded. Therefore, the risk factor that the investigators were trying to modify was absent in most participants. Furthermore, they excluded individuals who had a BP >140/90 mmHg; therefore, only one individual had left ventricular hypertrophy shown on a cardiac MRI scan. Essentially this study was that of primary prevention. In other words, the authors asked the following question: If phosphorus concentration was lowered within the normal range, would the left ventricular mass be reduced? It is quite likely that a much larger study would be needed to see such an effect.

Individuals with CKD who are likely to benefit from sevelamer or a phosphate binder are those who have hyperphosphatemia or secondary hyperparathyroidism. This study does not answer the question of whether treatment of hyperphosphatemia benefits the cardiovascular system. In other words, it did not ask the question of whether reducing the serum phosphorus concentration among individuals with CKD with hyperphosphatemia reduces left ventricular hypertrophy. Had the investigators studied people with progressive CKD who had both hyperphosphatemia and increased left ventricular mass, randomized them to either drug or placebo, and diligently reduced serum phosphorus concentration, an improvement in left ventricular mass and function may have been evident in 9 months. This is not what the study examined and therefore we are unable to answer this question.

Reviewing the pathophysiology of hyperphosphatemia in this context may also provide answers as to why this trial was null. In 1971, Slatopolsky et al. demonstrated that a stepwise reduction in nephron mass in dogs given a high-phosphorus diet (1200 mg/d) was associated with the development of secondary hyperparathyroidism. However, if phosphorus was restricted in their diets (100 mg/d), the decline in kidney function did not result in the development of secondary hyperparathyroidism. In the study by Chue et al., there was no decline in kidney function. It is possible that if the participants selected had proteinuria and progressive renal dysfunction, the development of secondary hyperparathyroidism may have occurred over a longer period of follow-up and differences between drug and placebo may have been manifest. In other words, stable kidney function is unlikely to affect left ventricular hypertrophy and mineral metabolism in a way that the authors intended.

In this study, the change in serum phosphorus concentration upon sevelamer administration was nearly nonexistent. In addition, the study did not influence vitamin D metabolism. It has long been recognized that dietary phosphorus intake modulates the synthesis of 1,25-dihydroxy vitamin D in healthy men and that the restriction of phosphorus in children with moderate CKD can restore the synthesis of 1,25-dihydroxy vitamin D. However, restriction required that dietary phosphorus be restricted to quite low levels (approximately 0.35 g/d). Information on dietary phosphorus intake was not available, but the study drug did not alter the mineral metabolism axis in a measurable manner. This may be another reason why the downstream consequences on the cardiovascular benefits were not observed.

In light of this study, should we abandon restricting dietary phosphorus in people with progressive CKD? In my opinion, the answer is no. As suggested by the Kidney Disease Improving Global Outcomes guidelines, it appears prudent to maintain phosphorus and calcium in the normal range, control secondary hyperparathyroidism, and maintain vitamin D sufficiency among individuals with progressive CKD.

This acronym for the study by Chue et al. was CRIB-PHOS. According to the Merriam-Webster dictionary, one definition of the term crib is a crèche. The Chue et al. study should not serve as a death knell to investigations on phosphorus in progressive CKD, but should instead serve as a crèche for future investigations on the value of phosphorus reduction in preventing cardiovascular disease and CKD progression. Although null, the study by Chue et al. has important lessons for the design of trials that extend beyond mineral metabolism. Compared with trials designed based on epidemiology alone, trials designed with a sound understanding of the biology and pathophysiology of deranged pathways may yield more desirable answers.

DISCLOSURES
R.A. is a consultant to Ardelyx, Astra Zeneca, Bayer, Daiichi Sankyo, Eli Lilly, Roche, Sigma Tau, and Takeda; serves on the speaker bureau of Merck and Abbvie, steering committees of Abbvie, Roche, and Reata, and the data safety monitoring boards of Amgen, Celgene, and La Jolla Pharmaceuticals; and has received research support from the National Institutes of Health, Department of Veterans Affairs, and Daiichi Sankyo.

REFERENCES

See related article, “Cardiovascular Effects of Sevelamer in Stage 3 CKD,” on pages 842–852.