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In Focus

Tip-toeing toward the finish line

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End-stage renal disease impairs functional status, diminishes quality of life and shortens lifespan. Despite recent improvements in survival of affected individuals in the USA, 50% of patients will die within 3 years of initiating hemodialysis [1]. Nephrologists, dialysis clinic providers, insurers and patients are all in need of therapeutic advances that can further impact mortality in this population. In the current era of growing emphasis on healthcare quality and safety and increasing attention to patient-centered outcomes, an ideal intervention is one that would safely improve clinical outcomes and have beneficial effects on the patients' overall health and well-being. This framework has fostered renewed vigor in addressing a long-standing question about the management of hyperphosphatemia in the dialysis population: what is the 'optimal' serum phosphate?

Large observational studies have repeatedly demonstrated a strong independent relationship between hyperphosphatemia and increased risk of mortality in patients undergoing dialysis treatment [2–4]. Experimental studies attest to the biological plausibility of these consistent epidemiologic findings. Phosphate excess has been implicated as a potent inducer of vascular calcification [5], which may contribute to increased rates of cardiovascular events and death through effects on arterial stiffness and left ventricular hypertrophy. However, randomized clinical trials evaluating the efficacy of lowering serum phosphate levels on reduction of mortality are lacking. Indeed, all phosphate binders in the USA have been approved solely on the basis of efficacy studies that demonstrated ability to reduce serum phosphate levels in hyperphosphatemic patients undergoing dialysis.

In this evidence-free zone, several well-designed pharmacoepidemiologic studies employing propensity score methods to address confounding by indication have expanded our knowledge base [6–8]. In a prospective observational cohort study of 8610 incident hemodialysis patients in the USA, initiation of treatment with phosphate binders during the first 90 days on hemodialysis was independently associated with an 18–30% lower risk of subsequent 1-year all-cause mortality compared with no early treatment [6]. The results were unchanged in an analysis that matched treated and untreated patients on their baseline serum phosphate levels and propensity score of receiving phosphate binders. A subsequent study using data from the prevalent European dialysis population followed for 3 years yielded similar findings [7]. In this prospective cohort of 6797 patients, propensity score-adjusted analyses also demonstrated a significant association between phosphate binder use and lower all-cause and cardiovascular disease mortality. Importantly, with the exception for aluminum-based binders, there were no major differences in associations with mortality by phosphate binder class, with the hazard ratios (HR) ranging from 0.28 to 0.73. In contrast, a propensity score-matched analysis conducted in another USA cohort of incident dialysis patients found no significant association between use of calcium-based phosphate binders and 1-year survival (HR 0.89; 95% confidence interval [CI], 0.72–1.10) [8].

In this issue of *Nephrology, Dialysis and Transplantation*, Komaba and colleagues extend the existing data by reporting the findings from 2269 prevalent dialysis patients in Japan and by focusing on lanthanum carbonate as the pharmacological exposure variable. Similar to prior studies [6–8], the authors used rigorous statistical methodologies to address confounding. Uniquely, the data set captured information immediately prior to and during market introduction of lanthanum carbonate in Japan. This allowed the authors to study incident users of lanthanum carbonate, capture covariate information immediately prior to exposure and generate a sufficient number of matched treated and untreated individuals. As expected, compared with

serum phosphate levels of 4.6 to 5.3 mg dL^{-1}, levels above 6.4 mg dL^{-1} were significantly associated with higher mortality during a mean follow-up time of 2.7 years. Following market introduction of lanthanum carbonate, its prescription increased gradually to 27% over 3 years. Lanthanum carbonate use was associated with ∼0.5 mg dL^{-1} decline in serum phosphate levels and gradual reduction in use of other phosphate binders. In propensity score-matched analyses, mortality was not significantly different in lanthanum carbonate users compared with nonusers (HR 0.71; 95% CI 0.47–1.09). However, among patients with serum phosphate levels of >6 mg dL^{-1}, the relationship was significant and favored lanthanum carbonate users (HR 0.52; 95% CI 0.28–0.95). As the authors suggest, the expected phosphate binding afforded by lanthanum carbonate and dietary liberalization are the most likely explanation for these new findings. These inferences are in line with the findings from the Dialysis Outcomes and Practice Patterns Study, which reported an association between favorable nutritional status, phosphate binder use and improved survival in hemodialysis patients [9]. The authors also acknowledge that reduction in calcium containing phosphate binder use may have contributed to the improved survival, a finding consistent with a recent comparative effectiveness analysis of calcium acetate versus sevelamer carbonate in elderly hemodialysis patients (n = 31 776), which demonstrated an improvement in survival with sevelamer carbonate (HR 0.94; 95% CI 0.91–0.98) in propensity-matched cohorts [10].

Taken together, these pharmaco-epidemiologic studies suggest the possibility of a survival advantage associated with phosphate binder use, particularly with non-calcium containing phosphate binders. However, because propensity score matching only allows for balancing of measured covariates, unmeasured differences between users and nonusers could still account for the observed results. Thus, we are left with the conclusion that existing observational data are inadequate to guide clinical decisions and that randomized, controlled clinical trials are needed to confirm or disprove the survival benefit related to phosphate binder use.

The burgeoning cost of phosphate binders (which is now estimated to be over $1.5 billion in the USA), an expanded number of 'novel' phosphate binders and a long absent consideration of patient-centered outcomes has re-focused awareness of the need for definitive trials in this area. Despite a lack of evidence on the efficacy of phosphate binders on hard clinical outcomes or on the clinical utility of strict phosphate control, over 80% of prevalent dialysis patients are prescribed phosphate binders [9, 11], and guideline groups recommend that the target serum phosphate should approach normal levels [12, 13]. However, achieving an unproven serum phosphate target may come at the cost of excessive pill burden [14], clinically important gastrointestinal side effects related to phosphate binder use, un-necessary restrictions on dietary and lifestyle choices, and labeling individuals who are unable to reach the desired target as noncompliant. In the USA, there is also the added financial cost related to co-payments. Finally, excessive amounts of calcium-based binders appear likely to contribute to vascular calcification, which is a risk factor for mortality [15, 16].

Given the dearth of evidence, the End Stage Renal Disease Quality Measure Development and Maintenance Mineral and Bone Disorder Clinical Technical Expert Panel convened by the Center for Medicare and Medicaid Services in 2013 recommended a randomized, controlled clinical trial to compare the effects of different serum phosphate targets on hard clinical outcomes (mortality, fractures, hospitalizations and cardiovascular events) in patients undergoing dialysis. Several other expert groups, including guideline work groups, have also endorsed this idea [17]. Recent developments in pragmatic clinical trial methodologies and funding initiatives for patient-centered outcomes research position the nephrology community and all the relevant stakeholders to step up to the plate and work together to deliver the high-level evidence that will inform clinical care decisions. Management of hyperphosphatemia in dialysis is fraught with evidence gaps. Chief among them is inattention to patient experiences with phosphate binders and dietary phosphate restriction. The next landmark study in this area must finally evaluate clinically relevant, rather than biochemical, outcomes and should address the long over-looked domain of patient-reported outcomes.

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CONFLICTS OF INTEREST STATEMENT

Dr Isakova received honorarium from Bayer, and Dr Block is a consultant for Keryx.

(See related article by van Komaba *et al.* Survival advantage of lanthanum carbonate for hemodialysis patients with uncontrolled hyperphosphatemia. *Nephrol Dial Transplant* 2015; 30: 107–114.)

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IN FOCUS

The kidney biopsy in lupus nephritis: time to move beyond histology

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The percutaneous kidney biopsy has been the gold standard for the diagnosis of lupus nephritis (LN) since before the original World Health Organization classification of LN in 1974 [1]. The incorporation of immunofluorescence and electron microscopy into kidney biopsy evaluation provided significant insights into the pathogenesis of LN. These and other insights from experimental models and clinical studies were driving forces behind the 2004 International Society of Nephrology (ISN) and Renal Pathology Society (RPS) reclassification of LN histology. An important goal of reclassification was to better align histology to treatment options and prognosis. The ISN/RPS classification introduced the subcategories of global (G) and segmental (S) to proliferative forms of LN and defined composite indices for active and chronic disease to better forecast outcomes [2]. Unfortunately, despite these efforts, very little improvement has occurred in our ability to accurately predict treatment response or determine long-term kidney outcomes by examining histology alone. This may be due, in part, to the fact that the histologic responses of the kidney to injury are limited, whereas the underlying molecular mechanisms of injury are quite heterogeneous in a disease like systemic lupus erythematosus. Much as the addition of immunofluorescence and electron microscopy to light microscopy advanced the field of renal pathology, integration of molecular analysis with kidney histology may better account for the heterogeneity of LN, and ultimately yield a superior classification scheme that will foster targeted therapeutic approaches and provide more reliable prognostic information. Here we consider 'molecular' to include gene, transcript and protein expression.

In this issue of the journal, Alaiya and colleagues attempt to differentiate Class IV-G from Class IV-S LN through a molecular (proteomic) approach and then correlate the