

Phosphate Binder Choice in Dialysis Patients: A Call for Evidence-Based Rather Than Marketing-Based Clinical Practice

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Which agent is optimal for phosphate binding in patients with kidney failure is one of the great contemporary debates in clinical nephrology. Ever since aluminum-based agents were discarded as mainstream therapy, calcium-based phosphate binders have constituted the standard phosphate binder therapy. More recently, calcium-free phosphate binders such as sevelamer and lanthanum have become available, and several more are in the drug development pipeline. At the core of the controversy about phosphate binder choice is the premise that some of the calcium in calcium-based phosphate binders is absorbed from the gastrointestinal tract, and is deposited in tissues—particularly in the heart valves and arteries, thus accelerating valvular sclerosis and arteriosclerosis and causing increased risk of cardiovascular disease and death. Several studies have demonstrated that vascular or valvular calcification scores, as assessed by electron-beam computed tomography, were associated with subsequent cardiovascular risk and mortality.¹⁻³ Small randomized studies comparing calcium-based phosphate binders and sevelamer have yielded conflicting results on the differential effects of these binders on calcification scores: some indicated a beneficial influence of sevelamer on these surrogate outcomes, but failed to conclusively demonstrate the mechanism.^{4,5} In particular, uncertainty remains as to whether these findings were attributable to sevelamer's lipid-lowering effects rather than to reduced calcium load. However, the biggest question from these trials was whether any deceleration of vascular calcification, as assessed by electron-beam computed tomography, would translate into improved patient outcomes. After

all, such calcification scores cannot determine the exact location of the lesion—in the intimal or medial layer of the vasculature. Thus, randomized trials comparing effects of calcium-based phosphate binders and sevelamer on clinical outcomes were conducted and the first results have become available this year. These trials are especially important in light of the substantially higher treatment costs with sevelamer.⁶

In this issue of *AJKD*, St. Peter and colleagues present a set of prespecified secondary analyses from the Dialysis Clinical Outcomes Revisited (DCOR) study,⁷ a randomized open-label study of sevelamer versus calcium-based phosphate binders in more than 2,100 long-term hemodialysis patients.⁸ Their study differs from the recently published primary analyses of DCOR in that follow up was not conducted through regular study visits, but rather by merging the DCOR analytical dataset with these patients' health care claims from the Centers for Medicare and Medicaid Services (CMS). While the primary analyses censored patients at 90 days after study discontinuation (with the intention to minimize crossover between treatment groups), this CMS-based analysis allows for an intention to treat evaluation, complete ascertainment of the primary endpoint (death from any cause), as well as to study the effect of treatment on health care utilization and economic outcomes from the payor's perspective.

In the original DCOR publication, Suki et al found that patients randomized to sevelamer experienced similar all-cause (hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.79 to 1.10) and cardiovascular mortality (HR, 0.93; 95% CI, 0.74 to 1.17) compared to those who received calcium-based phosphate binders.⁸ Intent-to-treat analyses based on CMS data revealed similar findings: all-cause (HR, 1.01; 95% CI, 0.89 to 1.16) and cardiovascular mortality (HR, 1.09; 95% CI, 0.90 to 1.33) did not differ between the treatment groups. This is important since the particular strengths of the analyses by St. Peter et al include greater ascertainment of the primary endpoint (857 deaths were recorded versus only 442 in the original DCOR manuscript), de-

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creased loss for follow up and, hence, more person-time available for study, all increasing statistical power. In this context, some had raised the possibility that DCOR was too underpowered to show the intended benefit of sevelamer.⁹ This is simply incorrect: the sample size calculation for DCOR assumed a 23% reduced mortality from sevelamer versus calcium-based phosphate binders,⁸ and the lower 95% CI that was actually estimated in DCOR was 0.79, clearly indicating that the trial was sufficiently powered to detect the prespecified benefit of 23% and effectively ruling out a benefit of that magnitude.

As similar as the 2 manuscripts are in their primary results, they do differ markedly, however, in their approach to subgroup analyses. Suki et al tested for interaction between several prespecified baseline variables and the treatment effect; among these, the interaction with age revealed a *P* value of 0.02.⁸ The authors then conducted age-stratified analyses and found that among patients 65 years or older, the sevelamer group experienced a 23% reduction in all-cause mortality compared to the calcium-based phosphate binder group. Similarly, St. Peter et al also detected this interaction between age and treatment, with a *P* value less than 0.01.⁶ But in contrast to the earlier report, they adjusted this *P* value for the number of interaction tests that were performed and found it no longer significant (*P* = 0.06). Thus, the conclusion that the authors of the 2 papers drew from essentially the same data and results differed fundamentally: the presence versus absence of greater efficacy of sevelamer in older patients. Interestingly, had Suki et al adjusted their *P* value for multiple testing, as done by St. Peter et al and appropriate as argued below, the *P* value for the interaction with age would have been approximately 0.1, also failing to indicate any treatment effect differences by age. Generally, without evidence of an interaction, the findings from the overall study cohort pertain to all subgroups within it. In DCOR, the null assumption of no benefit of sevelamer over calcium-based phosphate binders was not refuted. Therefore, the original DCOR publication did not demonstrate that sevelamer was superior to calcium-based phosphate binders—for the overall trial population, or for any subgroup of patients.

Clearly it is crucial to understand how such a discrepancy in interpreting essentially the same data can arise, especially with the enormous implications for clinical practice, drug reimbursement, and further research. Especially for the clinician who is being bombarded with promotional messages aimed at influencing their phosphate binder choice, understanding the technicalities of this argument is of paramount importance; we provide a brief explanation in the following section.

Subgroup analyses are frequently conducted and reported as part of clinical trial publications, but particular rules in the conduct and caveats in the interpretation of subgroup analyses apply, as recently reviewed by Lagakos.¹⁰ For example, an investigator may be interested in whether the relative efficacy of one intervention versus another differs between older and younger subjects. Perhaps the intervention is relatively efficacious in both groups, but more so among older patients (quantitative interaction). Alternatively, it is possible that the benefit is present in older, but absent in younger patients (qualitative interaction). Typically, several interaction tests are performed, with the undesired side effect that the conventional *P* value threshold for significance of 0.05, designed for a single hypothesis test, loses its appropriate interpretation. If several interaction tests are being performed, the likelihood of finding a *P* value below that threshold increases just by random chance, therefore increasing the probability of a false-positive finding. As a consequence, either the significance threshold or the *P* value need to be adjusted.¹⁰ This is what St. Peter et al appropriately did in their analysis, but in the original DCOR publication, such *P* value adjustment was not applied. The authors justified their nonadjustment for multiple testing by citing an important paper by Rothman, but seriously misinterpreted his argument.^{8,11} In no way did Rothman suggest adopting as evidence the findings that arose from analyses that were unadjusted for multiple testing. Rather, he argued that such signals had to be investigated further in subsequent studies that were specifically targeted at the suggested hypothesis.¹¹ In the case at hand this would mean conducting a prospective randomized trial of sevelamer ver-

sus calcium-based phosphate binders in dialysis patients older than 65 years, and then acting upon the evidence found.

The absence of any interaction for several baseline variables is also informative for putting the findings from DCOR into the context of results from a recently published subgroup analysis from the Renegel in New Dialysis (RIND) trial, a randomized open-label trial of the effect of sevelamer versus calcium-based phosphate binders on calcification scores.³ The RIND trial randomized 148 incident dialysis patients and found that sevelamer-treated patients experienced less progression of their coronary artery calcification scores over 18 months compared to patients treated with calcium-based phosphate binders.⁵ The secondary analysis included the 127 participants with baseline coronary calcification, and found a nonsignificant trend towards increased mortality in patients originally randomized to calcium-based phosphate binders (11 versus 23 deaths, $P = 0.06$). After adjusting for 9 additional baseline variables, the mortality difference for phosphate binder choice reached significance ($P = 0.02$), albeit from an overfitted model (a statistical phenomenon that can yield inflated effect estimates and unreliable confidence intervals).

Trying to reconcile the findings from DCOR and RIND, Suki and colleagues suggested the possibility that sevelamer may need to be introduced soon after dialysis initiation, and that it may have simply been too late for intervention in the DCOR participants, most of whom had been on treatment for several years.⁸ However, the absence of an interaction between dialysis vintage and treatment argues against such an interpretation: no evidence was found in DCOR that sevelamer was (more) efficacious among newer dialysis patients. Further, the strength of the evidence from the 2 publications certainly cannot be weighed equally: DCOR was a sufficiently powered, well-conducted, prospective randomized trial; whereas the RIND results (although intriguing) were derived from an extended follow-up of a subset of patients in the original trial, where randomized phosphate binder assignment ended after 18 months, and where the significance of the findings may have been driven by the analytical approach that was used. On the

other hand, since adjustment for baseline coronary artery calcification appears to have strengthened the association between sevelamer use and adverse outcomes in RIND, one might speculate that patients with greater calcification at baseline are more likely to derive clinical benefit from sevelamer.

Interestingly, and inconsistent with their approach to tests of statistical interaction, St. Peter et al did not adjust the analyses of relative health care and resource utilization in the DCOR cohort for multiple comparisons.⁷ While most outcomes were not affected by randomized treatment, the number of hospitalizations and hospital days were lower in sevelamer patients. The corresponding P values, however, were all very close to the prespecified significance threshold of 0.05 (the smallest was $P = 0.02$) and would have been rendered nonsignificant after multiple adjustments. Further, it appeared that the suggestion of reduced hospitalization was driven by infectious causes and “other” causes (hospitalizations not due to infection, vascular access, fracture, or cardiovascular disease), whereas the relative rate of hospitalization from cardiovascular causes was even closer to unity.⁷ These findings are surprising given the biological rationale favoring the use of a calcium-free phosphate binder—which would be expected to lead to reduce the risk of hospitalization for cardiovascular causes. In our opinion, a healthy dose of skepticism should be applied before taking these economic benefits at face value.

Nonetheless, St. Peter et al should be congratulated for their novel approach to ascertain clinical outcomes in study patients using a linkage to CMS data. Perhaps use of claims-based follow up will facilitate future randomized trials studies in the dialysis population or in elderly CKD patients. Using this method, large-scale studies could be conducted in a less expensive, independent, and unbiased way and might provide a solution to the often underpowered randomized efficacy trials of treatments in nephrology patients. User fees to the US National Institute of Diabetes and Digestive and Kidney Diseases could be imposed for investigators using this route, and these revenues could serve to augment the Institute’s funding of other clinical research in nephrology.

From the currently available evidence, several important questions remain regarding the relative efficacy of sevelamer compared to calcium-based phosphate binders. The benefits from sevelamer that were suggested in smaller studies using surrogate endpoints were not confirmed in a large state-of-the-art (albeit open-label) trial, which also seriously threatens the potential utility of electron-beam computed tomography-assessed calcification scores as surrogate endpoints.¹² Thus, the results of the DCOR study seem to suggest that a large clinical benefit of sevelamer is unlikely in unselected dialysis patients, although the findings from DCOR and RIND raise the tantalizing possibility of benefit in certain subgroups (such as new or older dialysis patients, or in those with greater vascular calcification). In addition, the findings of St. Peter et al raise the possibility that the higher medication costs of sevelamer might be wholly or partially offset by reduced hospitalization costs.

Nonetheless, these hypotheses need to be formally tested in sufficiently powered prospective trials, and considered unproven until clearly shown otherwise. Physicians, payors, and those who produce clinical guidelines should take note, and consider whether current practices for the prescription and reimbursement of sevelamer are overly liberal. Uncritical adoption and continued use of sevelamer would send the wrong signal to the pharmaceutical industry—a strategy of aggressive marketing should not be allowed to circumvent the requirement for sound science and conclusive evidence of benefit.

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