These potential benefits of newer agents, including sevelamer, and other anion-exchange resins, as discussed by Drs Wrong and Harland [5], are supported, only in part, by very large-scale observational studies, where lower levels of serum calcium, phosphorus, and less so parathyroid hormone, are associated with improved survival for people with chronic kidney disease [1,6]. As we have previously discussed extensively, this is not enough [7–9]. What remains important is that the direct relationship between modification of calcium, phosphorus or PTH with improved survival and cardiovascular outcomes in randomized, controlled trials is still far from proven. This is despite the largest trial in this area, the Dialysis Clinical Outcomes Revisited (DCOR) trial enrolling over 2100 patients to either sevelamer or calcium salts, which showed no difference for mortality between treatment arms [10] and the meta-analyses of phosphate binders [11], calcimimetics [9] and vitamin D compounds [8].

The ongoing search for efficacious and cost-effective agents, such as anion exchange resins, is laudable. Therefore, the suggestion of Wrong and Harland that colestipol, or other cheaper alternatives, could be promoted in preference to the more expensive sevelamer, is appealing. However, while these and other measures may be temporarily supported, the real priority for resources in this area should be directed at understanding the effects of the treatment for altered mineral metabolism on patient centred outcomes, including bone pain, cardiovascular events and mortality in chronic kidney disease. Do any of these drugs, which can control phosphorus levels, really have any effect on reducing the excess mortality which is attributable to high serum phosphorus levels in chronic kidney disease? Certainly there are numerous resins that can be used to absorb intestinal phosphorus, but just as well there are now numerous data to support that adequately powered, randomized trials investigating either pharmaceutical agents or the serum targets of calcium, phosphorus and parathyroid hormone levels should be developed.

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Time-dependent effect of sevelamer HCl on the cardiovascular system

Sir,

We read with great interest the paper ‘Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients’ by Tonelli and co-workers [1].

Although well written, we only partially agree with the authors’ conclusions. Indeed, our experience corroborates the notion of a significant time-dependent effect of sevelamer on the cardiovascular (CV) system. To our opinion, this represents a plausible explanation for the contradictory results of the RIND [2] and the DCOR study [3] and should be further emphasized.

We observed the effect of sevelamer HCl on cardiovascular morbidity (hospitalization rate and duration) in 16 patients (age: 67.4 ± 11.9 years) on maintenance dialysis (dialysis vintage: 167.4 ± 87.9 months). At study entry, phosphate binder regimen was changed from calcium salts to sevelamer HCl, and CV hospitalization events were collected thereafter for 3 years.

At study completion we noticed a significant reduction in serum calcium, phosphate, calcium × phosphate product and total cholesterol (all P values <0.05) (figure 1a). In contrast, non-significant changes in serum PTH and triglycerides were recorded.

More importantly, a graded decrease in the hospitalization rate (P < 0.01) and hospitalization duration (P < 0.001) was noted throughout the study follow-up (figure 1b). Of note, none of the bone mineral or lipid metabolism parameters was significantly associated with the reduction of the hospitalization rate and duration.

Indeed, our experience further supports the time–treatment interaction previously reported by other authors. In a post hoc analysis of the DCOR study, Suki and colleagues showed a significant improvement in survival
among patients treated for >2 years with sevelamerHCl as compared to peers treated with calcium salts (RR 0.66; IC 95%: 0.48–0.94; P = 0.02) [4]. Furthermore, as also stated by Tonelli et al. [1], the longer follow-up of the RIND study [2] appears as one of the main factors that explain the apparent discrepancies between the ‘positive’ data from the RIND study [2] and the ‘negative’ data from the DCOR study [3].

In light of these and our experience, it is therefore plausible that to impact CV morbidity and mortality in end-stage renal disease a longer time period of treatment might be recommended. Furthermore, although based on a very small sample size, it appears that the beneficial effects of sevelamerHCl rely on its pleiothropic effects [5] rather than on phosphate control only. However, future studies should confirm our preliminary data.

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Fig. 1. Mean levels of (a) calcium (Ca), phosphate (P) and calcium × phosphate (Ca × P) product and (b) the hospitalization duration and rate during the 3-year study.

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Reply

Sir,

We thank Dr Savica et al. for their interesting data. We agree that these statistically significant results are striking for such a small sample size (n = 16) and the findings are very different from those observed in the randomized DCOR study. We agree that the interesting results of Savica et al. should be confirmed in a much larger randomized trial.

We thank Dr Wrong and Dr Harland for their comments. We agree that there are several other promising candidate medications for use as phosphate binders in people with kidney failure and that colestipol is one such agent. However, colestipol would need to be studied in properly done randomized trials before its use could be recommended.

Although available evidence does not support the widespread use of sevelamer on either clinical or economic grounds, the theoretical rationale for the use of non-calcium-based binders remains compelling. We hope that the lessons learned from the DCOR, the RIND and other studies will stimulate the design and execution of new trials that determine whether sevelamer (or other non-calcium containing phosphate binders) have clinically meaningful effects—focusing on populations that may be likely to benefit. Until such time, it is very difficult to justify the use of sevelamer, especially in publicly funded health care systems.

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