Sevelamer: Where are the data?

To the Editor: In their study of sevelamer versus calcium-based phosphate binders in hemodialysis patients, Chertow et al [1], in a recent issue of *Kidney International* concluded that sevelamer attenuates vascular calcifications while maintaining good phosphorus control. The implications of this claim are exemplified by the aggressive marketing efforts of this study's sponsor, Genzyme Corporation [2].

Canavese et al [3] raised critical statistical issues regarding the study in their subsequent letter to *Kidney International*. They noted that "the patients cited in Tables 3 and 4 . . . are not the same," and that "multivariate analysis of the role of hypercalcemia and hypercalcemic episodes in the progression of calcification" was not provided. Neither point was addressed in the authors' reply [4].

The means and standard deviations of baseline electron beam tomography (EBT) scores (Table 3) document that score distributions were not comparable between groups. Furthermore, ~30% of the baseline cohort was excluded from the 26- and 52-week analyses. Without baseline distribution of EBT scores for the actual population analyzed, absolute or percentage changes cannot be determined. Further weakening the validity of this study's findings are the absence of evidence of the reproducibility of the EBT measurements and the failure to make appropriate statistical adjustments for subjects who dropped out of the study (Table 3, footnote). Those adjustments may reveal that even the primary end point, phosphorus control, was not achieved.

With provision of the data requested here and by Canavese, reanalysis may likely determine that there were no differences between absolute EBT scores of the two groups or in the changes in the 52-week EBT scores. Until these additional data are published in a transparent fashion, the authors' claim that sevelamer attenuates cardiovascular calcification remains purely speculative.

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Milking the sevelamer-calcium debate

We are delighted that the results of our randomized clinical trial comparing calcium-based phosphate binders with sevelamer [1] continue to be of interest to readers of *Kidney International,* prompting Letters to the Editor more than one year after the publication date. It is especially gratifying to read such a letter from Professor McCarron, a leading researcher who has published more than 200 articles over the past 20 years, including more than 150 on the topic of calcium.

Professor McCarron correctly summarized our conclusion, that relative to calcium salts, sevelamer attenuated the progression of coronary artery and aortic calcification, and indeed, sevelamer (and calcium) provided good control of serum phosphorus. Our initial reply to four letters to the Editor was necessarily brief; the major issues raised by Canavese et al [2] and other authors were addressed [3]. Herein we provide additional requested data.

If one were to consider only those 150 study subjects who underwent a follow-up electron beam tomography (EBT) scan, the baseline median (interquartile range) coronary artery calcium scores were 665 (79 to 2250) and 578 (76 to 1294) in the sevelamer- and calcium-treated subjects, respectively ($P = 0.30$). Corresponding median (interquartile range) aortic calcium scores were 668 (25 to 3662) and 360 (4 to 4030) ($P = 0.61$). These results are similar to the results for all study subjects who underwent baseline EBT scanning ($N = 186$) reported in Table 3.

Among calcium-treated subjects, the changes in coronary artery and aortic calcification were directly correlated with the time-averaged serum calcium concentration ($r = 0.18$ and $r = 0.28$, respectively). The median changes in calcification were significantly higher when the time-averaged serum calcium concentrations were greater than or equal to 9.5 mg/dL.

Professor McCarron claims that the validity of the study is weakened by the "absence of evidence of reproducibility of the EBT measurements." Indeed, in the manuscript we stated "the median inter-scan variability is 8% to 10% for the Agatston score" and we provided supporting references. Professor McCarron also contends that we failed to "make appropriate statistical adjustments for subjects who dropped out of the study" and that "those adjustments may reveal that even the primary endpoint, phosphorus control, was not achieved." In the manuscript we stated that "all laboratory analyses were performed using a last value carried forward approach," a conservative method commonly used to account for the analysis of continuous variables in a longitudinal study

[4]. Considering only measured serum phosphorus concentrations in the 150 subjects with repeat EBT, the time-averaged serum phosphorus concentrations were 5.3 ± 0.9 and 5.4 ± 1.0 mg/dL in the sevelamer- and calcium-treated groups, respectively ($P = 0.94$).

One wonders why Professor McCarron believes that "reanalysis may likely determine that there were no differences between absolute EBT scores of the two groups or in the changes in the 52-week EBT scores." These were precisely the analyses provided in [1], in as "transparent" a fashion as possible. Indeed, we specifically stated that "evaluation of the change in calcification was performed in several ways owing to imperfections of each approach" and that "we resolved to report absolute and relative effects . . . recognizing that qualitatively and quantitatively consistent results would be required for our conclusions to be robust." Could we have been any more transparent?

We were interested to learn of Professor McCarron's involvement with certain organizations whose interests might be furthered by trumpeting the benefits of calcium. According to the Center for Science in the Public Interest (CSPI) [5], Professor McCarron has served as Director of the Calcium Information Center, a joint project of Oregon Health Sciences Center, New York Hospital-Cornell Medical Center, and Memorial Sloan Kettering Cancer Center. The Calcium Information Center was funded in part by SmithKline Beecham, the maker of Tums® brand of calcium carbonate. CSPI also notes that Professor McCarron has received numerous grants from the National Dairy Council. A brief on-line tour reveals other industrial contacts, including Cole Bros. [6], a bottler of calcium-rich mineral water (sporting the highest calcium content of 15 brands shown). In addition to his role as Visiting Professor in the Department of Nutrition at University of California Davis (per the signature below the Letter to the Editor), Professor McCarron serves as President of Academic Network LLC, a healthcare telecommunications service bureau and consulting firm located in Portland, OR [7]. Academic Network, LLC counts among its clients Cole Bros., Dairy Management, Inc., and the International Dairy Foods Association. Kathleen A. McCarron is Chief Executive Officer of Academic Network, LLC.

While we welcome criticism of our work, we respectfully request that the pages of Kidney International, a prestigious journal on which we depend for accurate information, be used as a forum for the advancement of science, rather than as a battleground for industrial interests.

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