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.

David A. McCarron
Davis, California

Correspondence to David A. McCarron, M.D., FACP, Academic Network, 1221 SW Yamhill, Suite 303, Portland, OR 97205.
E-mail: dmccarron@academicnetwork.com

REFERENCES


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.