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**Reply**

We thank Dr Kahn for emphasizing the utility and limitations of assessing oedema and measuring body weight in the patient with hypernatraemia [1]. As illustrated in our [2] and other [3] studies, the calculation of a tonicity balance is another useful and feasible strategy to determine the basis of hypernatremia. We beg to differ regarding the effect of a sodium load on the serum sodium concentration in healthy volunteers. Andersen et al. demonstrated that a hypertonic sodium load of 3.85 ml/kg infused in 90 min caused the serum sodium to rise from normal to 146.2 ± 0.5 mmol/l [4]. Similarly, those patients in our study who developed hypernatraemia with a positive fluid balance (38% of total) also received mildly hypertonic solutions, while they at the same time had reasons to excrete a hypotonic urine and were unable to express thirst [3]. Other factors may also disturb renal water and salt handling during critical illness, for example activation of the renin–angiotensin system. Hypernatremia due to a positive sodium balance may be best treated with a combination of diuretics and electrolyte-free water.

**Conflict of interest statement.** None declared.

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**The CARE-2 study results: setting the record straight**

Sir,

We appreciate the comments made by Dr. Jurgen Floege [1] regarding our article [2]. In his editorial comments, he stated that, in our study, the beneficial effect of sevelamer was overrun by a higher prevalence of diabetic nephropathy and smoking among our patients. His statement that these calcification risk factors are unlikely to be affected by the choice of phosphate binders is a speculation that cannot be supported by evidence. Moreover, even if that statement were true, then results of the RIND trial should have also been different from the TTG and be similar to ours since the percent of patients with diabetic nephropathy in the RIND study was comparable to that in our study (54% versus 57%) [3,4].

A second point that he raised was that the proportion of patients lost to follow-up was higher in CARE-2 versus TTG (38% versus 30%; Table 2), rendering the interpretation of the CARE-2 outcome data somewhat more difficult than those of TTG. In fact, the proportion of dropout in the TTG was 34% at 12 months (68 of 200 patients). That is comparable to our dropout of 38%. The number of patients in the TTG study who had evidence of baseline coronary artery calcification (CAC) and was used in their famous Figure 1 (page 249 of the TTG article) was even smaller, probably around 50% of the patients [3]. These dropouts may indeed have had an impact on the results of both studies. However, we conducted several sensitivity analyses in order to assess the impact of missing data on our results. These included the use of multiple imputation, a standard statistical method for dealing with missing observations and an additional, ‘pessimistic’ analysis of missing values that imputed missing day 360 CAC scores as twice their last observed value for calcium acetate recipients but equal to their last value for sevelamer recipients. Qualitative and quantitative results of these two sensitivity analyses were similar to the results of the primary analyses that omitted the missing values. We believe that this sort of analysis is useful and could have been pursued by the authors of the TTG.

Thirdly, he stated that the increase in median calcification scores in the CARE-2 study revealed the same trend as in TTG, namely a lower rate of change in the sevelamer group. However, one should not only look at the numerical trend but also at the percentage increase in CAC score. In our study, the median percentage increases in CAC score were 29% in calcium acetate-treated patients versus 30% in those treated with sevelamer. Moreover, Dr Floege did not comment on the fact that, in the RIND study, in the subgroup of patients with detectable coronary calcifications at baseline (Agatston score > 30), the progression of calcification in sevelamer-treated patients was not statistically different from that of calcium-treated patients but was much higher than that reported from the TTG study. The 5% increase in CAC at 12 months in sevelamer-treated patients in the TTG study was unusually low if one compares that with the 38% progression at 18 months in the
RIND study and the 30% increase at 12 months in our study.

Fourth, he used the study by Russo et al. in patients with a GFR of \( \sim 30 \) mL/min to support his argument [5]. In that study, sevelamer retarded the progression of cardiovascular calcifications to a higher degree than calcium carbonate. However, we would like to draw his attention to the fact that in that study, despite calcium loading from calcium carbonate, progression of CAC was less than that in untreated patients suggesting that calcium did not contribute to progression of CAC, a conclusion that supports our results.

Fifth, although we concluded that the use of calcium acetate for control of hyperphosphataemia in haemodialysis patients over a 12-month period does not contribute to progression of CAC compared to sevelamer, we were careful to state that we cannot conclude that intensive lowering of LDL-C has influenced the rate of progression of calcification in our patients. This is because, despite excellent cholesterol control in both treatment groups, there was significant within-group progression of calcification, indicating that other factors are driving the progression of calcification. This relentless progression is likely due to several ureaemia-related factors such as the uremic milieu, high serum phosphorus, calcium and PTH, vitamin D, chronic inflammation, oxidative stress and others. Finally, Dr Floege also referred to oversuppression of PTH as a factor in the progression of cardiovascular calcification in our patients. However, while the PTH level was lower in the calcium acetate-treated patients, only 11% of calcium acetate and 9% of sevelamer-treated patients had PTH levels < 150 pg/mL (ng/L) at the end of our study.

Finally, if calcium binders contributed to progression of CAC, and that calcification increased the risk for cardiovascular events and death, then one would expect a difference in cardiovascular mortality between patients receiving calcium versus those receiving sevelamer. In contrast, results of the DCOR, the largest randomized outcome trial ever reported in dialysis patients, showed no significant difference in all-cause or cardiovascular mortality between these two classes of phosphate binders, despite claims to the contrary [6–9].

Conflict of interest statement. Dr W.Q. is a consultant and speaker for Fresenius Medical Care Advisory Board and on the speaker bureau. Dr L.R.M. is a paid consultant to Fresenius Medical Care. The results were reported in dialysis patients to the TTG or CARE-2 study. Patients with a GFR of \( \sim 30 \) ml/min (Russo et al.) or just starting dialysis (RIND) differ from the TTG or CARE-2 population in that they had more residual renal function and thus a better ability to, for example, excrete excess calcium loads. Also, in such patients the prevalence of low-turnover renal osteodystrophy, a known risk factor for cardiovascular calcifications, is lower than that in patients on dialysis for several years [1]. These and other factors will account for the universal observation that dialysis vintage is one of the most potent predictors of calcifications [2]. Thus, comparing CARE-2 and TTG patients to these other populations strikes me as a comparison of apples and oranges.

With respect to dropout numbers, Drs Qunibi et al. correctly comment that out of 200 randomized patients in the TTG study, only 132 underwent an EBCF-based quantification of coronary and aortic calcification at 12 months, i.e. dropout was 34%. However, note that of the 200 patients entering the study, 14 never had a baseline scan and, therefore, did not enter into the calculations. Thus, the relevant number is 132 patients with 12 months of follow-up out of 186 screened at baseline, i.e. the 30% dropout mentioned in my editorial comment.

1. Floege J. Calcium-containing phosphate binders in dialysis patients with cardiovascular calcifications: should we CARE-2 avoid them? Nephrol Dial Transplant 2008; 14: 1–3


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Reply

Sir,

I thank Drs Qunibi, Muenz and Diaz-Buxo for their stimulating comments to my editorial comment. In their letter, Drs Qunibi et al. repeatedly compare the RIND study or the study of Russo et al. with either the TTG or CARE-2 study. Patients with a GFR of \( \sim 30 \) ml/min (Russo et al.) or just starting dialysis (RIND) differ from the TTG or CARE-2 population in that they had more residual renal function and thus a better ability to, for example, excrete excess calcium loads. Also, in such patients the prevalence of low-turnover renal osteodystrophy, a known risk factor for cardiovascular calcifications, is lower than that in patients on dialysis for several years [1]. These and other factors will account for the universal observation that dialysis vintage is one of the most potent predictors of calcifications [2]. Thus, comparing CARE-2 and TTG patients to these other populations strikes me as a comparison of apples and oranges.

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