caution in high-risk patients and specify that there is no convincing evidence to go <130/80 mmHg in these categories. Thus, a first important simplification of hypertension guidelines would be to state that BP levels <140/90 mmHg should be achieved in all patients. We respectfully disagree on the suggestion of Dr Liebl that BP targets (rather than BP-lowering treatment) should be individualized in each individual patient.

One practical recommendation that should always be considered for the clinical management of hypertension is to suggest a closer scrutiny for coronary disease and renal failure and caution in lowering BP levels in patients with high-risk profile or diabetes. These cautionary recommendations may be made also for elderly individuals, for whom excessive BP reduction or more ‘ambitious’ BP targets may impair coronary circulation and renal or cerebral perfusion, rather than reduce hypertension-related burden of disease. In these patients, a therapeutic strategy based on the global cardiovascular risk reduction, as recommended by current European guidelines [6], rather than on intensive BP lowering may be more appropriate.

Conflict of interest statement. None declared.

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Is combined calcium/magnesium phosphate binder really noninferior to sevelamer hydrochloride?

Sir,

In a recent randomized controlled trial by De Francisco et al. [1], combined calcium acetate/magnesium carbonate (CaMg) phosphate binder was shown to be noninferior to the comparator (sevelamer hydrochloride) at controlling serum phosphorus levels at Week 25. Given that an efficient and relatively affordable drug would certainly be of great benefit to the majority of chronic kidney disease (CKD) patients, this report opens new horizons in this field. Nevertheless, a few issues with regard to the confirmation ‘noninferiority’ in this study should be discussed.

The primary outcome of this trial, evaluating phosphate control of the combination of two salts which both individually have been proven before, to be efficient phosphate binders is beyond any doubt, and we agree that phosphate control in uraemia is crucial [2]. However, the main rationale behind the combination of these compounds is to decrease the calcium load compared to the use of a single calcium-based binder. In addition, not only serum phosphate but all variables at play in CKD-Mineral and Bone Disorder (MBD) should be considered in order to confirm the noninferiority between the two drugs [3].

Although in the study by De Francisco et al. [1] ionized serum calcium did not differ between groups, total serum calcium increased significantly in the CaMg group, accompanied by an asymptomatic increase in serum magnesium, while parathyroid hormone (PTH) decreased.

Hence, when considering also these parameters, and not only hyperphosphataemia, one could argue that there is no equality between both treatment arms. Indeed, according to the recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [4], one should strive towards sustained control of as many as possible variables for as long as possible. In this regard, the conclusion that one variable was well controlled in the CaMg group versus four in the sevelamer group might have been a more impartial conclusion than the one that was held now.

Second, according to the same KDIGO guidelines, trends should be preferred to isolated values to obtain a satisfactory control of mineral parameters. Also in this regard, the continuous reduction of PTH and increase in magnesium levels as observed in the study by De Francisco et al. [1] is important to be considered. A rise in serum Mg might be beneficial in the context of atherosclerosis, vascular calcification and cardiovascular risk [5]. However, if it is accompanied by a reduction in PTH and an increase in serum calcium, an adynamic bone status and/or mineralization defects could be generated [6]. It was not the aim of the study by De Francisco et al. [1] to investigate bone histology, and the authors were careful enough to point out this shortcoming, but as a consequence, this important question remains unsolved. A similar decline in PTH could have had even more dramatic consequences to the bone if the studied

doi: 10.1093/ndt/gfq810
population would have had PTH levels at baseline within the Kidney Disease Outcome Quality Initiative reference range (150–300 pg/mg) [7].

Finally, another concomitant effect which was not discussed in the publication by De Francisco et al. [1] but with an important potential on survival outcomes was the control of LDL cholesterol and potassium levels which is superior with sevelamer hydrochloride.

With regard to the tolerability profile, one could debate about the study design with sevelamer hydrochloride as a comparator when the improved formulation of sevelamer carbonate was already available on the market or at least was on the verge of being introduced.

In conclusion, the study by De Francisco et al. [1] adds valuable information with regards to calcium/magnesium phosphate binding in a socioeconomically affordable way. However, this trial, based on soft end points, should be considered with care since the choice of those end points and the conclusions seem to be slightly biased in favour of the investigational drug.

Conflict of interest statement. None declared.

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doi: 10.1093/ndt/gfq778

Advance Access publication 21 February 2011

Reply

Sir,

We thank Profs Spasovski and Vanholder for their interest in our study [1].

In their letter, the authors question the use of the term ‘non-inferiority’, as it relates to serum phosphorus levels only. In their opinion, the non-inferiority hypothesis should consider all variables that play a role in chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD). This is, however, difficult, as non-inferiority and its margins also relate to the study hypothesis and the calculation for the number of patients to be included into the study. As such, the assumptions may be correct for one parameter, however, they may not apply for another. Therefore, in clinical study practice, the study design of pharmaceutical studies is set up to demonstrate efficacy and is bound to use one primary objective. Thus, it is not easily feasible to design a non-inferiority study that equally examines all relevant variables possibly important to the development of CKD-MBD. In such a case, other statistical methods, such as adjustment for multiple testing with adaptation of patient numbers, would have been necessary.

In addition, Spasovski and Vanholder claim that our study is based on ‘soft endpoints’. However, the non-inferiority hypothesis to prove efficacy was clearly defined in the study protocol prior to study start by a change in serum phosphorus level of ≤0.15 mmol/L at Week 25 equating non-inferiority. We do of course agree that every conclusion derived from a study may raise several new questions.

It is correct that total serum calcium significantly increased in the CaMg group (0.071 ± 0.179 mmol/L in the CaMg group versus 0.004 ± 0.152 mmol/L in the sevelamer group). Yet, it should be noted that in comparison with studies where pure calcium salts were administered, the observed increase is minimal and the treatment difference between the two groups is also very small (0.0477 mmol/L). Furthermore, Kidney Disease: Improving Global Outcomes (KDIGO) states that: ‘In patients with CKD Stages 3–5D, we suggest maintaining serum calcium in the normal range (2.2–2.6 mmol/L) (2C)’ [2]. At Week 25 of our study, total serum calcium in the CaMg group was 2.219 ± 0.157 mmol/L versus 2.189 ± 0.157 mmol/L in the sevelamer group. Therefore, in both groups, mean calcium values were within or at the lower end of the recommended Kidney Disease: Improving Global Outcomes (KDIGO) ranges. Furthermore, the number of patient visits with serum calcium above the target/normal range (Kidney Disease Outcome Quality Initiative (KDOQI) >2.37 mmol/L or ULN: >2.6 mmol/L) [3] did not differ between treatment groups. In addition, and more importantly, ionized serum calcium was not different between treatment groups.

Spasovski and Vanholder also raise issues related to the reduction in intact parathyroid hormone (iPTH). It is important to note, that at screening, the mean iPTH value was ∼350 pg/mL. Before the patients received the study