

“Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis”

Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M, Lok CE, Fitchett D, Tsuyuki RT.
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In 2009 Jamal *et al.* could find no statistically significant difference in the meta-analysis of cardiovascular mortality and coronary artery calcification, between chronic kidney disease (CKD) patients receiving calcium-based compared with non-calcium-based phosphate binders. Conclusions were that there were still potentially important beneficial effects and that further randomized trials were required¹.

This meta-analysis was updated in a recently published paper in “The Lancet”². This report included a systematic review of articles published in any language after August 1, 2008 up until Oct 22, 2012. Eligible studies, determined by consensus with pre-defined criteria, were reviewed, and data were extracted onto a standard form. This search identified 847 reports, of which eight new studies (five randomized) met the inclusion criteria and were added to the ten studies (nine randomized) included in a previous report of the same group¹. Analysis of the 11 randomized trials that reported an outcome of mortality showed a significant reduction of all cause mortality of 22% in the patients assigned to a non-calcium containing binder compared to those assigned to a calcium-containing phosphate binder.

The methodological quality of this work is absolutely unquestionable. Clearly this publication is important, adds one more piece to the puzzle, and deserves some thought.

Phosphate-binder therapy for hyperphosphataemia is crucial for the treatment of patients with chronic kidney disease – mineral and bone disorder. Non-calcium-containing phosphate binders are increasingly favoured since calcium-based agents potentially

cause calcium overload and vascular calcification that confound the benefits of controlling serum phosphorous. Several non-calcium-containing phosphate binders are available in clinical practice, including the non-absorbed agent, sevelamer, and the absorbed agents, e.g., lanthanum.

The effects of sevelamer on the bone and vascular axis, and potentially its pleiotropic effects, may translate into clinical benefits. The beneficial effect of sevelamer on mortality was never definitely proven in a prospective, randomized, controlled study. This hypothesis is supported by data from several large studies that have shown improved clinical outcomes with sevelamer versus calcium. The RIND (Renagel in New Dialysis) extension study showed a lower rate of mortality in new dialysis patients treated with sevelamer versus calcium-containing binders³. Important considerations to this report have been raised by others⁴: This conclusion results of a *post hoc* analysis of a study designed to follow patients exiting a randomized trial once therapies are unrestricted and unblinded; considered non-interventional, open-label, prospective; no data on potential confounders such as LDL, Ca, phosphate or PTH; small number of patients; examining mortality as a secondary outcome. Clearly the RIND study results should be considered hypothesis-generating.

The Dialysis Clinical Outcomes Revisited (DCOR) trial was a multicentre, open-label study that included 2100 haemodialysis patients⁵. Patients were randomized to receive sevelamer or calcium-based phosphorus binders. The primary outcome was all cause mortality. The DCOR trial was negative for the primary outcome and found no differences in all cause

mortality for the overall study population of prevalent dialysis patients. The DCOR study showed improved mortality rates in predetermined secondary analysis. The elderly subgroup over 65 years and in those with at least 2 years follow-up had a significant decrease in mortality⁵.

These two studies demonstrated potential differences in clinical outcomes between non-calcium and calcium-based phosphate binders.

Although, no prospective outcomes studies have been designed specifically to address the effects of lanthanum carbonate on mortality, a *post-hoc* survival analysis was undertaken versus standard therapy⁶. This analysis suggested that lanthanum carbonate may offer survival benefit in dialysis patients over 65 years of age, but was insufficiently powered to determine differences in patients with > 2 years treatment. Given the retrospective nature of this study, further prospective trials are needed to confirm whether there is a survival benefit in patients treated with lanthanum.

With this background in mind, it seems to me that the use of a meta-analysis for the evaluation of a subject that was already studied with randomised controlled trials needs to be critically considered and should be interpreted with a great deal of caution. In an interesting editorial⁷ the authors state that “to cultivate a balanced approach to understanding results generated by meta-analysis of data from small trials it is important to accept the limitations implicit in this method”.

In my view meta-analyses only generate hypotheses and certainly should be carefully interpreted.

The present study contains important results supporting a benefit on mortality for the patients treated with non-calcium versus calcium-containing phosphate binders. However, one should always keep in mind that well designed randomised controlled trials are the strong basis for evidence-based medicine.

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