Author's response to reviews

**Title:** The Efficacy and Safety of Lanthanum Carbonate on Chronic Kidney Disease Mineral and Bone Disorder in Dialysis Patients: A Systematic Review

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**Version:** 4 **Date:** 13 September 2013

**Author's response to reviews:** see over
Dear Prof. Bjorn Meijers:

Thank you very much for the careful evaluation of our systematic review and for the useful suggestions. The responses to your questions are listed below.

1. **Major compulsory revisions**

   The authors have addressed my major concerns. Despite the authors' claim that the manuscript has been redrafted, the manuscript needs some language corrections before it can be accepted for publication.

   **Author’s response:** We have carefully checked this article and corrected the language mistakes.

2. **Minor Essential Revisions**

   Abstract:

   - **Results:**
     * LC can decrease serum phosphorus level and Ca×P product compared with placebo. I would suggest rephrasing: LC decreased…as compared to…

       **Author’s response:** The fragment has been changed into “LC decreased…as compared to…”

     * “in lowering vascular calcification or cardiovascular events, improving bone morphology or metabolism, improving bone turnover parameters.” Please change into “in lowering…events and improving bone morphology, bone metabolism, or bone turnover parameters.”

       **Author’s response:** This phrase has been changed into “in lowering…events and in improving bone morphology, bone metabolism, or bone turnover parameters.”

     * People treated…abdominal pain were observed. “were observed” is redundant.

       **Author’s response:** We have deleted “were observed.”

     * “Both the contents of lanthanum in blood and bone were under the limit of quantification which would be harmful to body”. Please rephrase (e.g. accumulation of LC in both blood and bone were below toxic levels).

       **Author’s response:** This phrase has been changed into “Accumulation of LC in blood and bone was below toxic levels.”

   Background:

   - First paragraph: * 40% patients, please change into “40% of patients”

       **Author’s response:** It has been changed into “40% of dialysis patients”

   Methods:

   - Interventions: * other medications can…change into could

       **Author’s response:** It has been changed into “could.”
* Dietary restriction was not mandatorily required...change into “not mandatory.”

**Author’s response:** It has been changed into “not mandatory.”

- Outcome: Calcium instead of callcium

**Author’s response:** It has been changed into “calcium.”

- Quality assessment: “will be” resolved, better change into were/would be

**Author’s response:** It has been changed into “were”.

- Data extraction: If the studies showed the results just with diagrams whose data cannot be collected… I suggest rephrasing (e.g. only displayed the results within diagrams of which data could not be retrieved)

**Author’s response:** It has been changed into “For studies that only displayed results within diagrams from which data could not be retrieved.”

- Statistics: please rephrase using uniform verb tenses (past)

**Author’s response:** Thank you for the reminder. We have changed the verb forms into that of the past tense in this section.

**Results:**

- characteristics of study: please leave “Error! Bookmark not defined”

**Author’s response:** We did not find the “Error! Bookmark not defined” comment. It may have been caused by the settings of Microsoft Word.

- effect on biochemical parameters: “And there was no difference when LC compared with CC group”, please change into “was compared” (see also other sentences in the current draft)

**Author’s response:** We changed all instances of this phrase into “was compared” in the draft.

- bone disorder: “Participates in three studies [20-22] performed at least once bone biopsy”, please change into ‘received at least one bone biopsy/once a biopsy)

**Author’s response:** It has been changed into “Three studies [20–22] involved participants who received at least one bone biopsy.”

- side effects: “LC appeared a higher rate of vomiting”, please change into “there was a higher rate… in patients treated with LC.”

**Author’s response:** It has been changed into “When compared with CBBs, there was a higher rate of vomiting … in patient treated with LC. Our meta-analysis also showed that when compared with NCBs, there was a lower rates of intradialytic hypotension … in LC-treated patient.”

**Discussion:**

- “The meta-analysis did not show lanthanum decrease all-cause mortality or cardiovascular events”, please change into did not demonstrate “that” (see also other sentences in the current draft)

**Author’s response:** Thank you for the reminder. We have checked the entire article.
and made the necessary corrections.

Conclusion:
- “without elevation the serum calcium level”, please change into “elevating”

**Author’s response:** It has been changed into “elevating.”

Figure 1
Please make this figure more concise and uniform (e.g. delete “0 citations from others sources”, …)

**Author’s response:** We deleted the “0 citations from others sources” and made the necessary corrections to the figure to ensure conciseness and uniformity.

References
Ref 23 and 31: leave out *

**Author’s response:** It has been removed.

Reference in between reference 23 and 24 has not been numbered
Ref 31: reference info repeated

**Author’s response:** Refs. 23 and 31 contained the repeatedly reported studies. We used this form according to the Cochrane Library guidelines. However, we believed that this form would confuse the reader. Thus, we numbered the repeated studies, relisted the references, and included “After excluding 2 repeatedly published studies [24, 31], 16 studies were identified and retained…” in the Results section.

Ref 44: Typo: Main author is Evenepoel and typo: Kidney int should be Kidney Int

**Author’s response:** We deleted this reference when we modified this part.

Quality of written English: Not suitable for publication unless extensively edited.

**Author’s response:** We have extensively edited the entire article by correcting the spelling and grammar mistakes and by improving our writing to meet the standards for publication.

Answers to Francesco Locatelli

Dear Prof. Francesco Locatelli:

Thank you so much for the careful review and very good suggestion to our systematic review. The response to your questions was list below.

The authors should delete the definition of new drug for Lantanum and Sevelamer because they are available since many years in many country.

**Author’s response:** We removed the descriptions of the new lantanum and sevelamer drugs from the article.

Moreover, more caution should be used in saying that the bone concentration of Lantanum is safe on the long term.

**Author’s response:** Thank you for the suggestion. We agree that caution should be
exercised in drawing conclusions.

In the Abstract, we changed ‘LC was safe for dialysis patients especially in patients with high risk of hypercalcaemia except for a higher incidence of vomiting’ as “Current evidence does not show a higher rate of adverse effects for LC compared with other treatments, except for a higher incidence of vomiting. Moreover, LC accumulation in blood and bone was below toxic levels.”

In the Discussion section, we deleted “and that both compounds were safe” from ‘Overall, the systematic review showed that SH and LC were comparable treatments for controlling serum phosphorus and calcium levels.”

In the Conclusions section, we added “In addition, comparison with sevelamer carbonate, safety in bone and liver, … should also be concerned in the future studies with LC.”

The positive effect of Sevelamer on lipids and inflammation in comparison to Lantanum should be better underlined.

Author’s response: We added the following in the discussion: Sevelamer binds to bile acids probably because of its physiochemical similarities to common bile sequestrants. This characteristic allows sevelamer to interfere with fat absorption and reduce LDL cholesterol levels [45]. In addition, sevelamer can physicochemically bind to the negatively charged lipid A portion of endotoxin (ET). In vitro experiments showed that SH can bind to ET in a dose-dependent manner [46]. Moreover, an in vivo experiment demonstrated that sevelamer can reduce ET which was triggered by renal failure [47]. Previous trials [48–50] showed that compared with calcium-containing phosphate binders, sevelamer reduces the levels ET and proinflammatory markers such as CRP, interlekin-6, endothelin-1, and plasminogen activator inhibitor-1 in dialysis patients. In patients with early diabetic CKD, sevelamer carbonate significantly reduces HbA1c, fibroblast growth factor 23, lipids, tumor necrosis factor-α, and oxidative stress compared with CC [51]. However, the studies included in our systematic review did not compare the anti-inflammatory effects of LC and SH. Compelling preliminary data demonstrate that the ET-binding effect and anti-inflammatory activity of SH are associated with the improvement of mortality in ESRD compared with those of calcium-containing phosphate binders [52]. Long-term clinical trials must be conducted to confirm the relationship between the
amelioration of lipid metabolism and the improvement of patient survival. In particular, we recommend that additional studies be performed to determine if the lipid-lowering effect or anti-inflammatory activity of SH can improve the clinical outcome for CKD–MBD patients compared with LC.

No discussion about the liver concentration and possible toxicity is presented.

**Author’s response:** We added the following in the discussion: In addition to that in bone, lanthanum accumulation in the liver should also be a point of concern because LC is excreted through bile. Although increased liver lanthanum deposition after oral lanthanum loading in uremic rats in comparison with normal renal function rats was observed[55, 56], a subsequent investigation showed that lanthanum was present in the lysosomes of hepatocytes and was mostly concentrated in the biliary poles of the hepatocytes and within the bile canaliculi [57]. No lanthanum was detected in the hepatocyte mitochondria, nucleus, or cytoplasm. The six-year, long-term clinical observation also showed that liver enzymes did not increase, and that the few cases of liver- or biliary-related adverse events, none of which were considered to be related to lanthanum, were mainly observed in the first two years of treatment [54]. However, one case study reported that lanthanum induced abnormal liver function in one male patient with PD and in one female patient with HD [58]. Our systematic review cannot provide sufficient evidence to show the safety of lanthanum in liver function. Therefore, future studies should also investigate the concentration and possible toxicity of lanthanum in the liver.

Please correct "concent" in "content in many parts of the manuscript.

**Author’s response:** We replaced “concent” with “content” in three places in the draft.