Effect of Calcium-based Phosphate Binders Versus Sevelamer on Mortality of Patients with Hemodialysis: A Meta-analysis

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Keywords. sevelamer, calcium acetate, cardiovascular system, renal dialysis, meta-analysis.

Chronic kidney disease is a public health problem. The purpose of this study was to compare the effects of sevelamer and calcium-based binders on mortality of hemodialysis patients.

PubMed, EMBASE and Web of Science were searched for related articles published before May 14, 2020. We included six studies with 43330 participants, of which 21147 and 22183 received calcium-based phosphate binders and sevelamer, respectively.

In the analysis of unadjusted data, sevelamer could lower cardiovascular mortality. When adjusted HRs was pooled, the cardiovascular mortality did not differ significantly in the sevelamer and calcium-based phosphate binders groups. Additionally, the all-cause mortality rate in sevelamer group was different from that in calcium-based phosphate binders group. However, sevelamer could not lower all-cause mortality in terms of the adjusted data. No significant difference was found in calcium and phosphorus between calcium-based phosphate binders and sevalmer. Sensitivity analysis showed that partial results of the study were inconsistent. There was no difference in the effect of sevelamer and calcium-based phosphate binders on the risk of all-cause mortality in patients with hemodialysis, after adjusting confounders. However, given the instability of the results, the results need to be further confirmed by a large sample and high quality RCTs.

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INTRODUCTION

Chronic kidney disease is a public health problem.[1] Hyperphosphatemia, a common complication of hemodialysis patients, is attracting more and more attention.[2] Elevated blood phosphorus levels play a key role in mineral and bone metabolism disorders.[3,4] Previous evidence[5,6] have recommended that correction of hyperphosphatemia should be attempted through a balanced approach of dietary phosphate restriction and phosphate-binders administration. Almost all dialysis patients require the addition of a phosphorus binder to control blood phosphorus.[7] According to the time sequence of production, the phosphorus binders can be divided into traditional phosphorus binders (containing aluminum and calcium and phosphorus) and new phosphorus binders (not containing aluminum and calcium and phosphorus). Despite both have similar phosphate-lowering ability, their effects on clinical outcomes remain unclear.[8]

Predominant pharmacologic therapy for hyperphosphatemia is a calcium-based phosphate binder (such as calcium carbonate or calcium acetate).[9] But, excessive calcium may exacerbate

vascular calcification.[10] The clinical practice guideline of 2017 Kidney Disease[11] Improving Global Outcomes (KDIGO) suggests restricting the use of calcium-based phosphate binders in patients with end-stage renal disease (ESRD) irrespective of baseline calcium levels.

Sevelamer is a non-calcium and non-absorbed phosphate-binding polymer. Some studies[12-20] have focused on the effect of sevelamer on coronary artery calcification (CAC), arterial stiffening, and electrocardiogram abnormalities. Among of those, one meta-analysis[16] showed that sevelamer benefited dialysis patients in terms of aortic calcification score (ACS), coronary artery calcification score (CACS) and hypercalcemia. Two reviewers[19, 20] considered the effect of calcium-based phosphate binders on mortality, cardiovascular events and vascular calcification. The result showed that treatment with sevelamer had no effect on cardiovascular calcification. Zhang *et al.* (2010)[18] demonstrated that there was no statistically significant difference in cardiovascular mortality and CAC in patients receiving calcium-based phosphate binders. Obviously, there are still some controversies about sevelamer, which need to be further explored.

Several clinical trials[21-26] have compared sevelamer and calcium-based phosphate binders in terms of mortality in hemodialysis patients. The results of these studies are inconclusive. Some studies[22,26] showed that sevelamer decreased the risk of mortality in patients with hemodialysis. However, some studies[21,23-25] showed that the mortality wasn't significantly different in sevelamer and calcium-based phosphate binders. In this study, we aimed to assess the efficacy of sevelamer and calcium-based phosphate binders on mortality in patients with hemodialysis. Especially, after adjusting the confounder factors (such as age, race, gender, diabetes, baseline CAC score, and so on) to accurately identify whether the use of sevelamer confers a significant survival benefit.

MATERIALS AND METHODS

Search Strategy

We did a systematic review in accordance with the Preferred Reporting Items for Systematic reviews and meta-Analyses (PRISMA) guidelines. PubMed, EMBASE and Web of Science were searched for related articles published before May 14, 2020. Keywords included "sevelamer", "renagel", "calcium phosphate", "calcium phosphates", "calcium acetate", "calcium ethanoate", "acetic acid calcium", "acinetobacter calcoaceticus", "calcium carbonate", "calcium-containing phosphate binders", "calcium-based phosphate binders", "hemodialysis" and "hematodialysis".

Inclusion Criteria

1) Types of studies: randomized, controlled trials (RCTs) or observational cohort study; 2) Patients: adults with hemodialysis, regardless of nationality, gender and race; 3) Intervention: compared sevelamer and calcium-based phosphate binders on mortality in patients with hemodialysis; and 4) Outcomes: CV mortality and all-cause mortality.

Exclusion Criteria

1) CV mortality or all-cause mortality wasn't reported; 2) the study design is not rigorous (the non-standard outcome measures, unclear or incomplete sample data); and 3) Unable to access original data.

Data Extraction

Two researchers independently screened relevant literature according to the inclusion criteria. Two researchers firstly reviewed titles and abstracts to find possibly related literature. Then, the full texts were scanned to identify whether it fits the pre-defined inclusion criteria. Discrepant opinions on study inclusion were resolved by discussing or consensus with the third researchers. The following information was extracted: first author, country, year of publication, study design, number of study participants, mean age, confounder adjustment. The cochrane risk of bias tool[27] was used to access the quality of studies.

Statistical Analyses

Statistical analysis was performed by STATA 15.0. All cause and cardiac vascular mortality was used for the outcome measures. Unadjusted and adjusted outcome measures were pooled in the meta-analysis. Unadjusted means of the crude model without any other factor correction, while adjusted HRs mean in the model other factors adjusted.[24] Dichotomous data were analyzed using Odds Ratio (OR) and 95% confidence intervals (95% CI). Risk estimates was assessed using Hazards Ratio (HRs) and 95% CI. Heterogeneity was evaluated statistically by heterogeneity X^2 (Cochran Q) and I^2

statistics. Sensitivity analysis was used to analyze the stability of the results of meta-analysis. A random effects model was utilized if the studies exhibited at least moderate heterogeneity ($I^2 > 50\%$). Otherwise, the fixed-effects model was selected.

RESULTS

Study Characteristics

A total of 85 literatures were obtained through the search strategy. After scanning the title and abstract, 79 articles were excluded for the following reasons: 1) Articles were repeated (n = 33); 2) Not comparing the sevelamer and calcium-based phosphate binders on mortality (n = 20); 3) Commentary or review (n = 6); 4) Studies on pharmaceutical economics (n = 3); 5) Participants were not hemodialysis patients (n = 10); and 6) Data was incomplete (n = 7). As such, we included six studies[21-26] in this meta-analysis (Figure 1). Table 1 details characteristic of including studies.

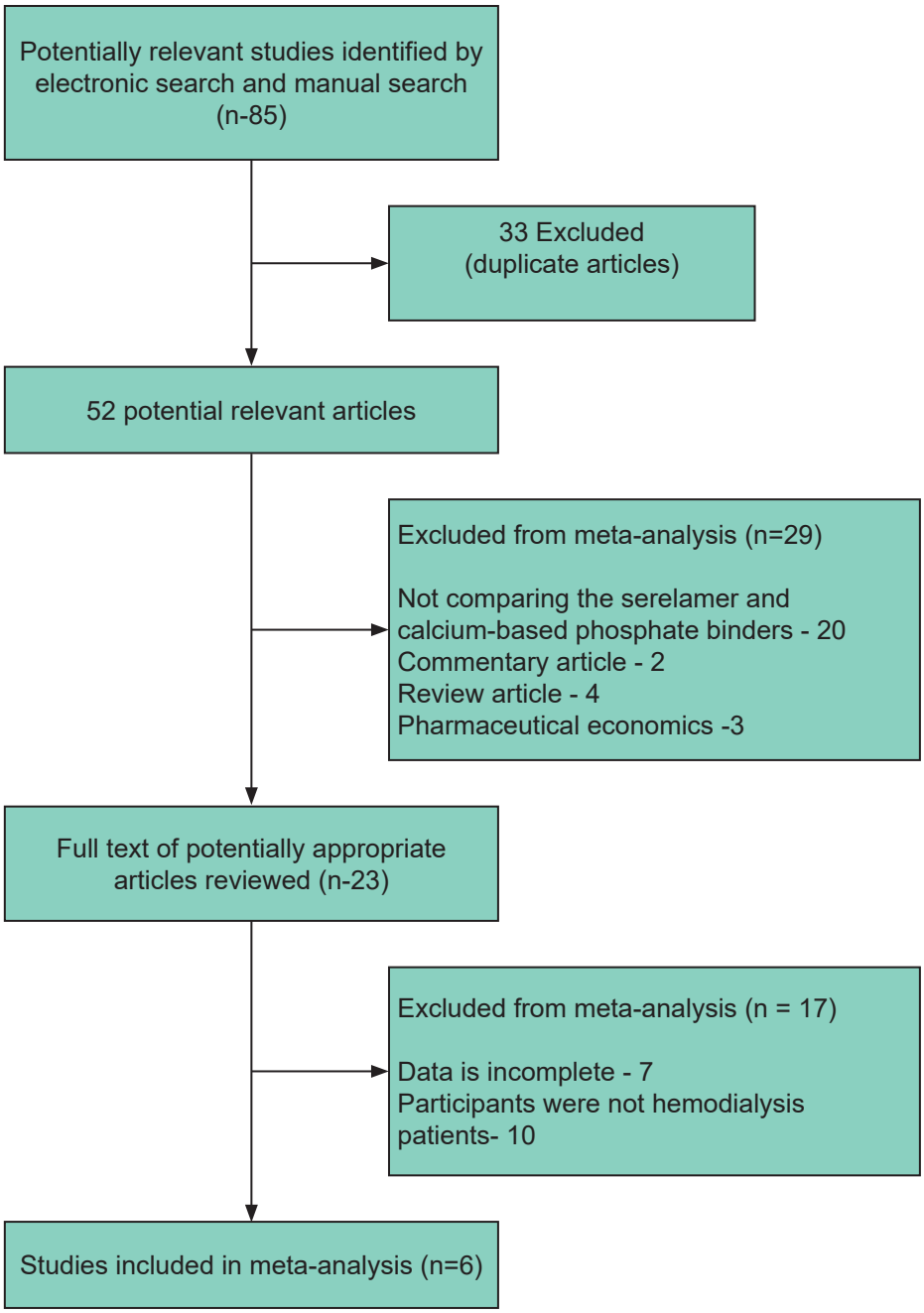

Figure 1. Flow diagram of search results and selection of including studies.

The Detailed Characteristics of Included Studies

Study	Country	Study Design	Number of Participants	Participants	Mean Age of Participants (in years)	Confounder Adjustment
Julia Spoendlin (2019)	America	cohort study	Sevelamer 2639 Calcium acetate 2065	USRDS linked to Medicare claims data (2012.05.01-2013.12.31)	Sevelamer 75.6 ± 6.9 Calcium acetate 75.5 ± 7.1	Demographics,ESRD- and HD-related covariates,proxies for socioeconomic status (eg, employment status, low-income subsidy status) and frailty (eg, inability to ambulate, status of institutionalization, comorbidity index), cardiovascular disease, comedication, and health care use covariates.
Akeem A. Yusuf (2014)	America	cohort study	Sevelamer 16916 Calcium acetate 18335	USRDS linked with Medicare Part D (prescription drug) (2006.07.01-2011.03.31)	Sevelamer 75.6 ± 6.6 Calcium acetate 75.4 ± 6.5	age; sex; race; ethnicity; cause of end-stage renal disease; dialysis vintage; hematocrit value; vascular access type; baseline treatment with erythropoiesis-stimulating agents, vitamin D, β blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/renin inhibitors, calcium channel blockers, statin, and cinacalcet; baseline hospitalizations; and baseline comorbid conditions.
Biagio Di Iorio (2013)	Italy	RCT	Sevelamer 232 Calcium Carbonate 234	patients recruited from 18 centers in Italy (2007.01-2008.09)	Sevelamer 66.6 ± 14.1 Calcium Carbonate 64.6 ± 15.4	baseline CAC score, serum phosphorus level, and C-reactive protein level
Guillaume JEAN (2011)	France	cohort study	Sevelamer 247 Calcium Carbonate 432	Patients were extracted from the Association Régionale des Néphrologues OStéodystrophie database (ARNOS), which includes information on patients in 25 dialysis centers in the Rhône-Alpes area (2005.07-2009.01)	Sevelamer 66.4 ± 13 $CaCO_3$ 68.9 ± 14	age, cardiac disease, gender, diabetes, dialysis session length, BMI, median serum level of 25-OH vitamin D, serum level of PTH, total calcium, phosphate, and albumin
Wadi N. Suki (2008)	America	RCT	Sevelamer 1053 Calcium salts 1050	patients at 75 dialysis centers within the US (2001.03-2002.01)	Sevelamer 59.9 ± 14.3 Calcium 60.1 ± 15.2	race, age (< 65 or ≥ 65 years), sex, diabetes status, primary cause of ESRD (diabetes, hypertension, or other), and dialysis vintag
GA Block (2007)	America	RCT	Sevelamer 60 Calcium salts 67	129 adult subjects new to hemodialysis were randomized in blocks of 10 and stratified by diabetic status to receive different treatment (2000.09-2002.12)	Sevelamer 56 ± 14.8 Calcium salts 58 ± 14.8	age, race, gender, diabetes, history of atherosclerotic cardiovascular disease, C-reactive protein, albumin, Kt/V, and baseline CAC score

Six studies included 43330 participants, of which 21147 received calcium-based phosphate binders (calciumacetate or calcium carbonate or calcium salt) and 22183 received sevelamer. Of the six[21-26] including studies, three were observational cohort studies, three were randomized controlled trials. Among six studies, four were conducted in the United States; and one study was conducted in Italy and France respectively.

Study Quality

Two independent researchers evaluated the quality of the primary studies using the Cochrane risk of bias tool. The evaluation items included seven parts: sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other sources of bias (other bias). Each aspect had three levels: "Low risk", "Unclear risk" and "High risk" (Figure 2).

Clinical Outcomes

Cardiovascular Mortality. There are four studies[21-23,25] that reported the unadjusted HRs for CV mortality between the sevelamer and calcium-based phosphate binders. Our results showed that sevelamer was associated with lower CV mortality

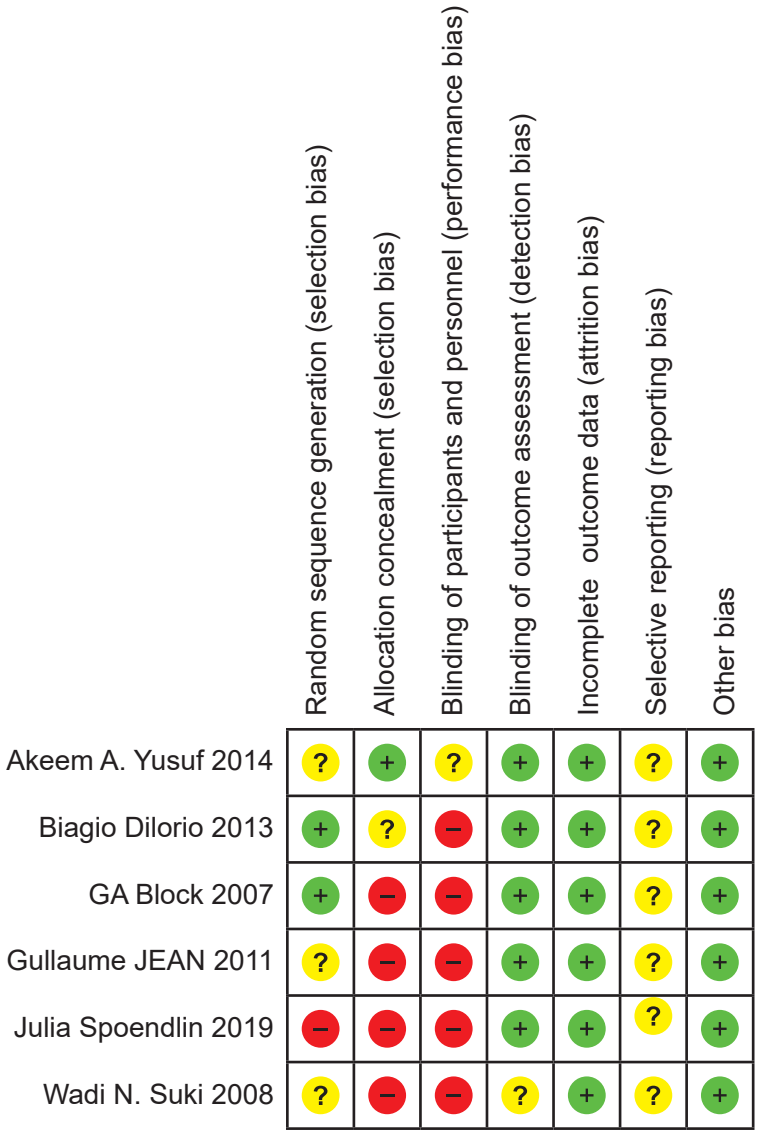

Figure 2. The risk of bias assessments for studies

compared with calcium-based phosphate binders patients in unadjusted Cox models (HR = 0.72, 95% CI: 0.53 to 0.99; $P < .05$, Figure 3). Heterogeneity was highly significant ($I^2 = 94\%$, $P < .001$). There are two studies[21,22] that reported the adjusted HRs for CV mortality between the sevelamer and calcium-based phosphate binders. Our results showed that the CV mortality rate for sevelamer patients was not significantly different from the rate for calcium-based phosphate binders patients in multivariable adjusted Cox models (HR = 0.34, 95% CI: 0.04 to 2.93; $P > .05$, Figure 4). Heterogeneity was highly significant ($I^2 = 97\%$, $P < .001$).

Sensitivity Analyses. We excluded each of the included studies of sensitivity analysis to verify the stability of the results. After one study[22] was removed, the results changed significantly. The results showed that the CV mortality rate for sevelamer patients was not significantly different from the rate for calcium-based phosphate binders patients in unadjusted Cox models, (HR = 1, 95% CI: 0.96 to 1.05; $P > .05$, Figure 5). Heterogeneity was not significant ($I^2 = 0\%$). However, when the other studies were stripped out one by one, there was no substantial change. This result indicates that the stability of the results of the meta-analysis is not good, and this study plays a significant role in the meta-analysis, which may change the final results.

All-cause Mortality. There are five studies[21-23,25,28] that reported the unadjusted HRs for all-cause mortality comparing the sevelamer and calcium-based phosphate binders. Our results showed that the all-cause mortality rate for sevelamer patients was significantly different from the rate for calcium-based phosphate binders patients in unadjusted Cox models (HR = 0.77, 95% CI: 0.6 to 0.99; $P < .05$, Figure 6). Heterogeneity was highly significant ($I^2 = 91.4\%$, $P < .001$). There are two studies[21,22] that reported the adjusted HRs for all-cause mortality comparing the sevelamer and calcium-based phosphate binders. Our results showed that sevelamer was not associated with lower all-cause mortality compared with calcium-based phosphate binders in adjusted Cox models (HR = 0.51, 95% CI: 0.14 to 1.86; $P > .05$, Figure 7). Heterogeneity was highly significant ($I^2 = 97.6\%$, $P < .001$).

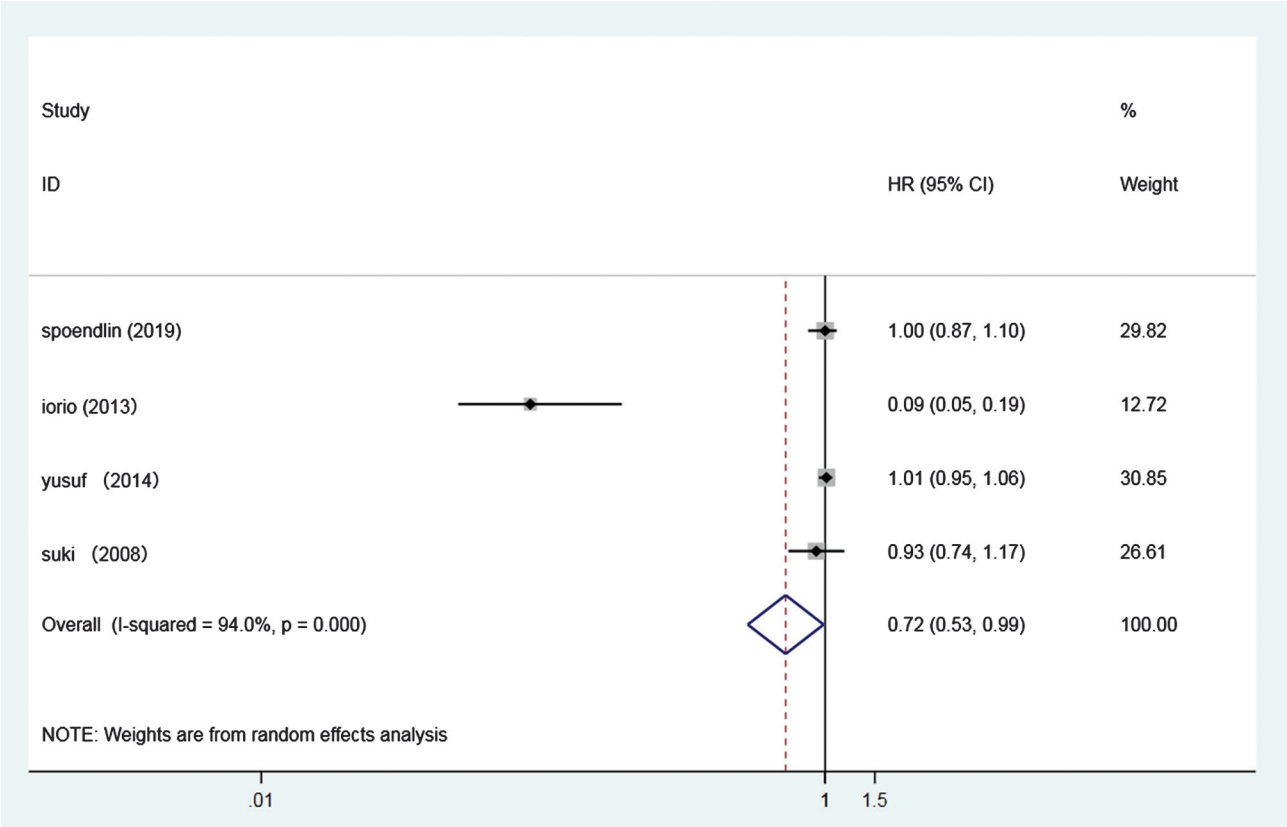

Figure 3. Unadjusted HRs for CV mortality comparing the sevelamer and calcium-based phosphate binders

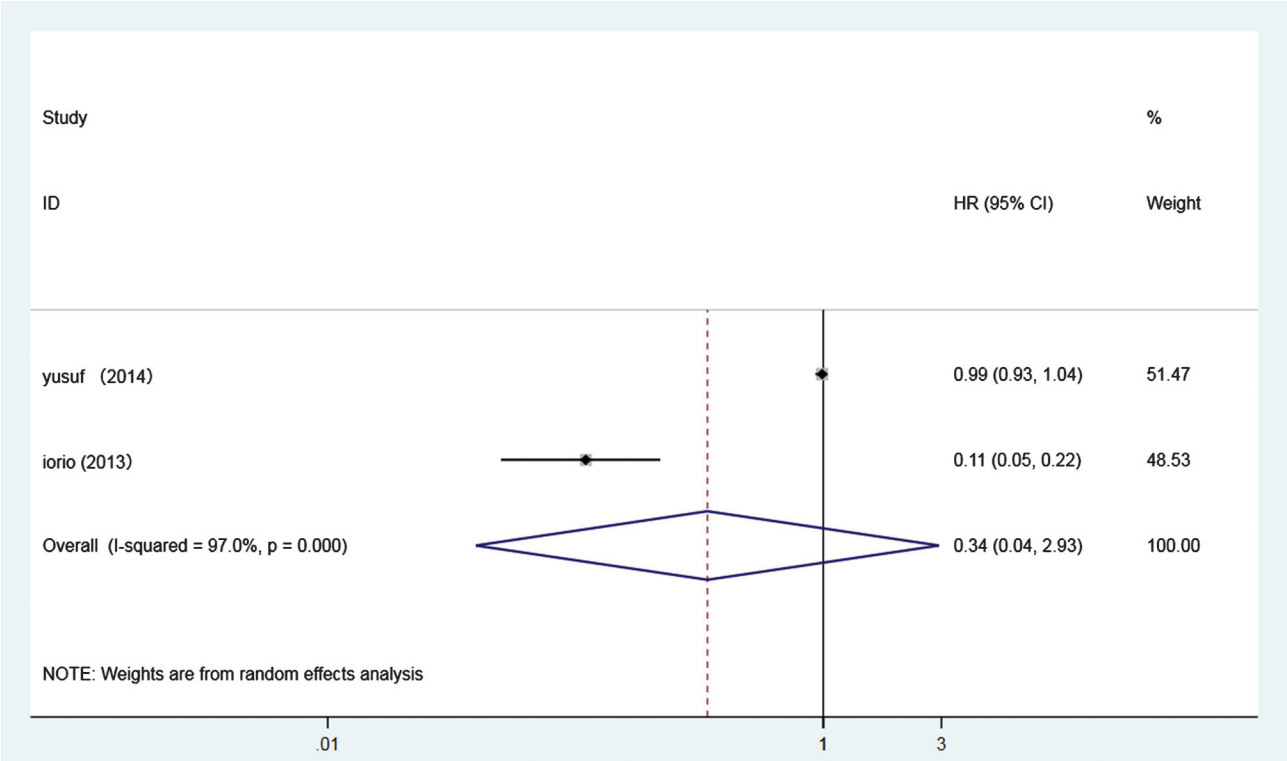

Figure 4. Adjusted HRs for CV mortality comparing the sevelamer and calcium-based phosphate binders

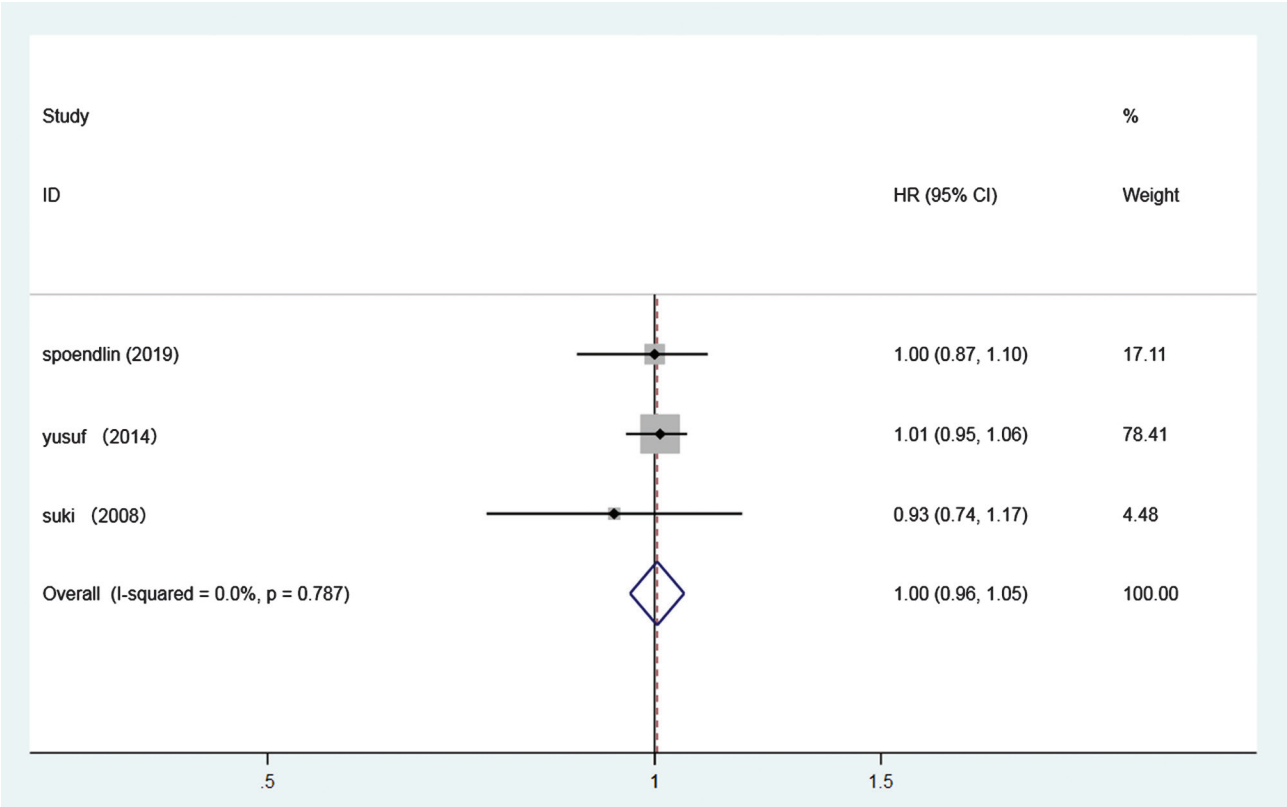

Figure 5. Results of sensitivity analysis for CV mortality without adjustment for confounding factors

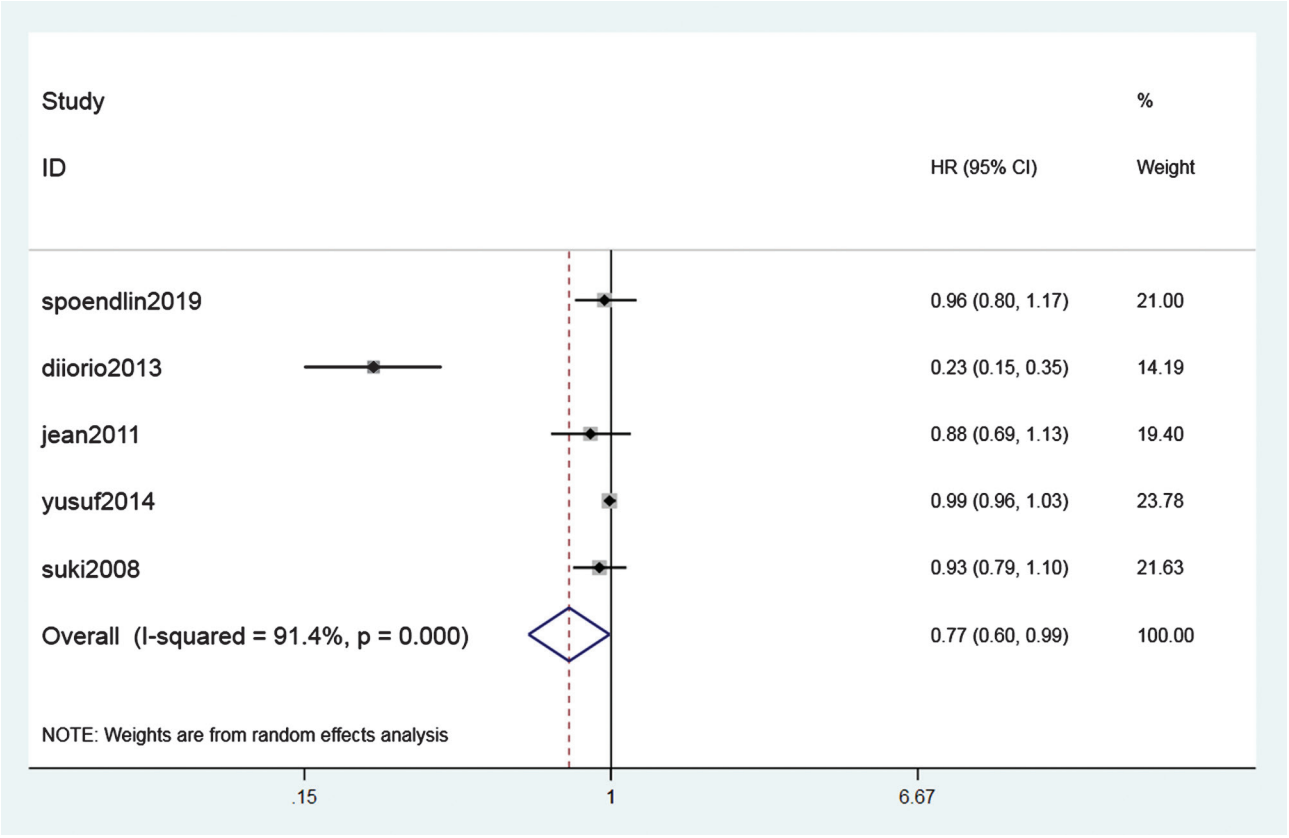

Figure 6. Unadjusted HRs for all-cause mortality comparing the sevelamer and calcium-based phosphate binders

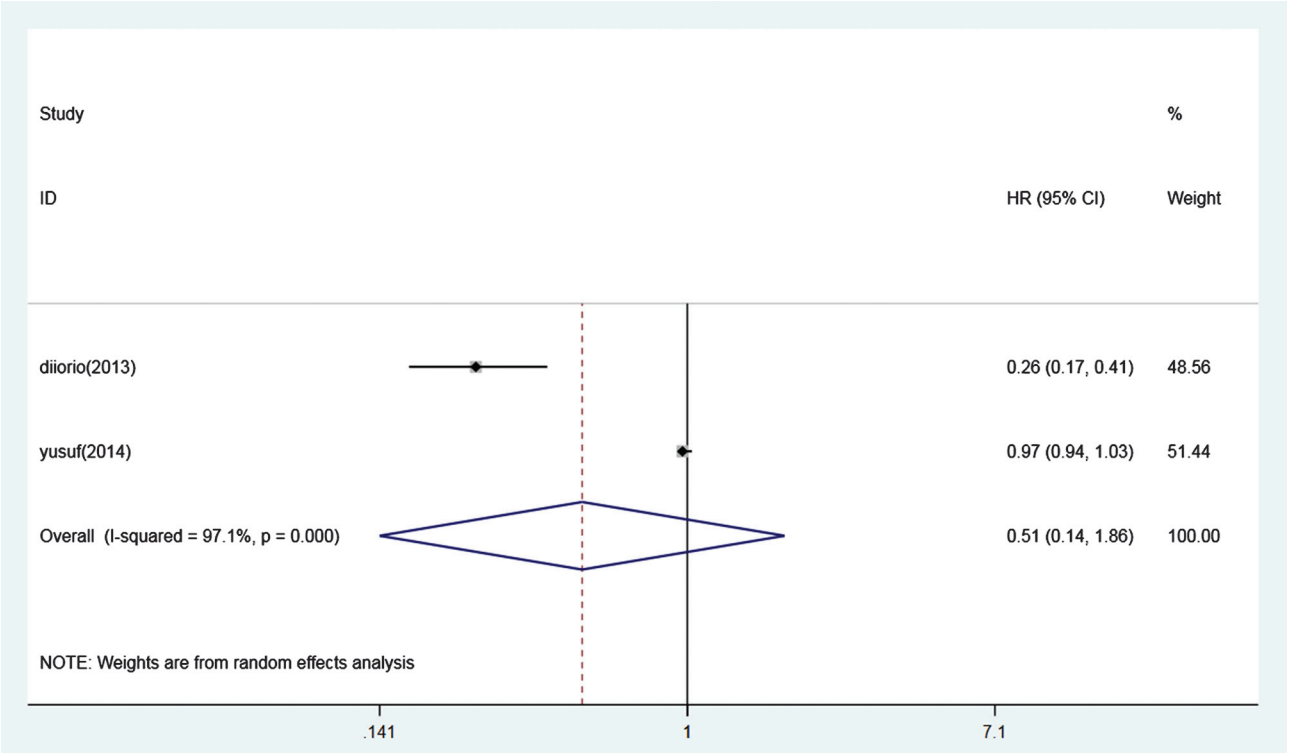

Figure 7. Adjusted HRs for all-cause mortality comparing the sevelamer and calcium-based phosphate binders

Sensitivity Analyses. We excluded each of the included studies of sensitivity analysis to verify the stability of the results. After one study[22] was removed, the results changed significantly. The results showed that the all-cause mortality rate for sevelamer patients was not significantly different from the rate for calcium-based phosphate binders patients (HR = 0.98, 95% CI: 0.95 to 1.02; $P > .05$, Figure 8). Heterogeneity was not significant ($I^2 = 0\%$). However, when the other studies were stripped out one by one, there was no substantial change. This result indicates that the stability of the results of the meta-analysis is not good, and this study plays a significant role in the meta-analysis, which may change the final results.

Effect on Calcium, Phosphorus and iPTH

As showed in Figure 9, two studies[22,25] reported the effect of sevalamer versus calcium-based phosphate binders on serum calcium. There was no evidence of difference on serum calcium between calcium-based phosphate binders and sevalmer (SMD = -0.22, 95% CI: -0.5 to 0.37; $P > .05$). The heterogeneity of this outcome was significant (heterogeneity χ 2 = 96.9%, $P < .001$). Two studies[22,25] reported the effect of sevalamer versus calcium-based phosphate binders on serum Phosphorus. There was no evidence of difference on serum phosphorus between calcium-based phosphate binders and sevalmer (SMD = -1.03, 95% CI: -2.21 to 0.15; $P > .05$). The heterogeneity of this outcome was also significant (heterogeneity χ 2 = 99%, $P < .001$). Two studies[22,25] reported the effect of sevalamer versus calcium-based phosphate binders on serum iPTH. In Iorio's study,[22] serum iPTH levels reduction were significant in sevalmer but not the calcium-based phosphate binders study arm (120 [78 to 137] vs. 240 [142 to 398], $P < .001$). In suki's study,[25] serum iPTH levels reduction were significant in sevalmer but not in the calcium-based phosphate binders study arm (278 [200 to 476] vs. 226 [142 to 387], $P < .001$). As the value of serum iPTH level was not reported as mean ± standard deviation and was not pooled in our meta-analysis.

DISCUSSION

In this meta-analysis, we identified six studies[21-23,25,26,28] comparing sevelamer and calcium-

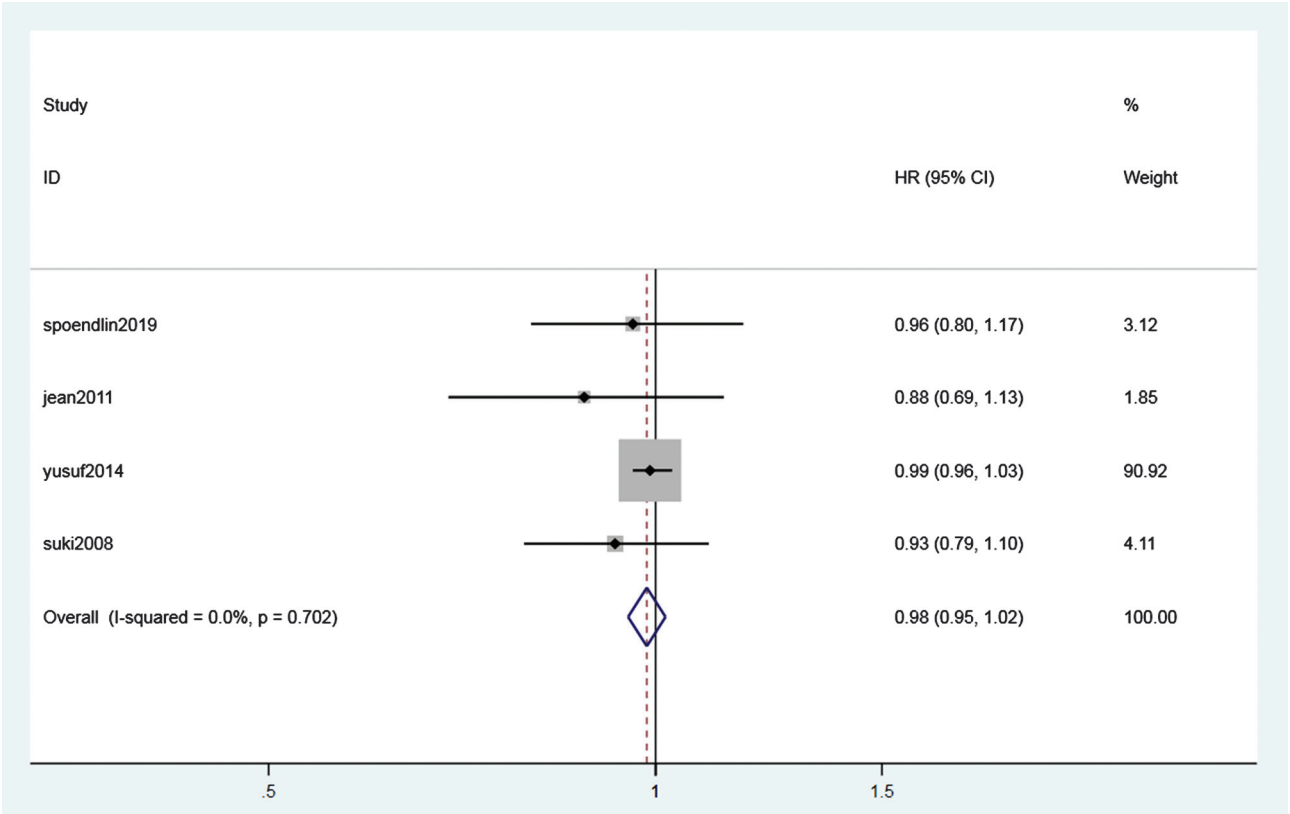

Figure 8. Results of sensitivity analysis for all-cause mortality without adjustment for confounding factors

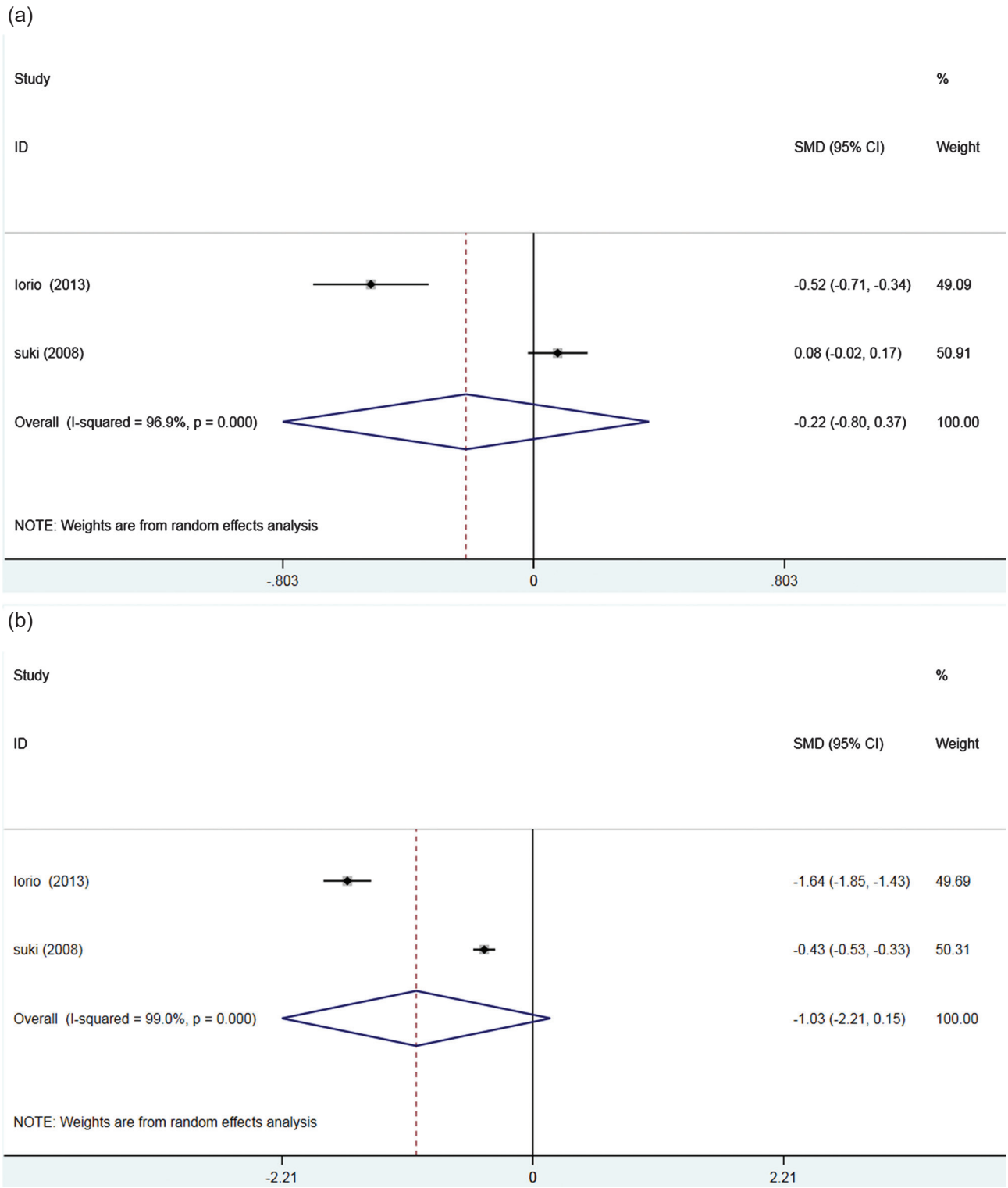

Figure 9. Forest plot of serum mineral metabolism between sevalamer and calcium-based phosphate binders: (a) serum calcium; (b) serum phosphorus (iPTH: intact parathyroid hormone)

based phosphate binders in terms of mortality in hemodialysis patients. Sevelamer group experienced lower cardiovascular mortality in an analysis of unadjusted data. However, when adjusted HRs was pooled, the cardiovascular mortality did not differ significantly in the sevelamer and calcium-

based phosphate binders groups. In addition, the all-cause mortality rate for sevelamer patients was significantly different from that in calcium-based phosphate binders patients. On the contrary, sevelamer group experienced no significantly different from all-cause mortality. Thus, the results of significantly different in our unadjusted analyses may be attributed to confounding factors.

The recommendations of more restricted calcium-based phosphate binders use in the 2017 updated version of the KDIGO guidelines. Even so, we can find the conclusion is based on weak evidence (grade 2B) consisting of 3 open-label RCTs with inconsistent results comparing clinical outcomes between sevelamer and calcium-based phosphate binders.[29] Previous meta analyses[16,19,30] also had different results for mortality rates. Sophie *et al* (2013)[19] showed that non-calcium-based phosphate binders were associated with a decreased risk of all-cause mortality in patients with chronic kidney disease. Suetonia *et al* (2016)[30] showed that sevelamer was related to lower all-cause mortality. A meta-analysis[31] published in 2015 showed that patients with CKD Stages 3 to 5D receiving sevelamer had lower all–cause mortality. These results are consistent with our results. However, Wang *et al* (2015)[16] showed that there was no significant difference in all-cause mortality between the calcium-based phosphate binders and sevelamer. The difference in the results may be that only three trials were included to access mortality. Too small study populations may cause bias. In the analysis of CV mortality, our result is similar to previous meta-analysis. In terms of cardiovascular mortality, all meta-analyses[16,19,30] have showed that no significant differences between sevelamer therapy and calcium-based phosphate binders therapy. Sevelamer may reduce cardiovascular mortality in the long-term. Significant evidence was observed for cardiovascular mortality, which also confirms this idea.

In the analysis of the effects of sevelamer on mineral metabolism parameters, a meta-analysis[19] published in 2009 showed that sevelamer reduced phosphorus and without altering serum calcium. Burke *et al*.[13] showed that sevelamer treatment was associated with a 2.14 mg/dL drops in serum phosphorus. This meta-analysis found a significant difference in the effect of sevalamer versus calcium-based phosphate binders on serum phosphorus and did not find a significant difference. However, it remains to be elucidated due to a paucity of literature.

Several previous meta-analyses have compared the mortality of patients with CKD treated with sevelamer or calcium-based phosphate binders. But, no meta-analsis has examined patients with hemodialysis using sevalamer on mortality. Thus, this is probably the first meta-analysis evaluating CV mortality or all-cause mortality in patients with hematodialysis treated with sevelamer or calcium-based phosphate binders. What is more, we also explored whether the survival benefit was independent and not modulated by other factors. Our meta-analysis has several strengths. We include a large sample to examine the mortality of sevelamer for hemodialysis patients. We took into account the influence of confounders, although many of them are currently inconsistent.

Several limitations should also be considered. Firstly, most of the hemodialysis patients were over 60 years old. Thus, our results can't be applied to young hemodialysis patients. Secondly, two studies[22,25] are open-label design, which might have introduced bias and influence the observation of the true treatment effect. Thirdly, despite our use of adjusted HRs to account for the effect of potential confounders, factors (such as baseline CAC score) were not collected, which may have affected the results. At the same time, this meta-analysis has significant heterogeneity and the sensitivity analysis found that Iorio study was the cause of greater heterogeneity, which may arise from the variety of baseline information of participants among the included studies. Fourth, we were unable to determine the effect of sevelamer on serum levels of phosphate and calcium. Anyway, we took care to reduce the likelihood of bias by following recommendations for the conduct of meta-analysis,[32] which may lead to robust conclusions.[33]

CONCLUSION

Compared with calcium-based phosphate binders, sevelamer has no advantage in terms of CV mortality and all-cause mortality. These results further question the advisability of using calcium-based phosphate binders as first line therapy. However, due to the confounding factors can't be unified, and most of the studies were open experiments. The results were not stable. Additional

large randomized controlled trials are needed.

ACKNOWLEDGEMENTS

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