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Original Investigation

Association of Drug Effects on Serum Parathyroid Hormone, Phosphorus, and Calcium Levels With Mortality in CKD: A Meta-analysis

Suetonia C. Palmer, MBChB, PhD,[1] Armando Teixeira-Pinto, PhD,[2] Valeria Saglimbene, MSc,[3] Jonathan C. Craig, MBChB, PhD,[2] Petra Macaskill, PhD,[2] Marcello Tonelli, MD,[4] Giorgia de Berardis, MSc,[5] Marinella Ruospo, MSc,[3,6] and Giovanni F.M. Strippoli, MD, PhD[2,3,7]

Background: Serum parathyroid hormone (PTH), phosphorus, and calcium levels are surrogate outcomes that are central to the evaluation of drug treatments in chronic kidney disease (CKD). This systematic review evaluates the evidence for the correlation between drug effects on biochemical (PTH, phosphorus, and calcium) and all-cause and cardiovascular mortality end points in adults with CKD.

Study Design: Systematic review and meta-analysis.

Setting & Population: Adults with CKD.

Selection Criteria for Studies: Randomized trials reporting drug effects on biochemical and mortality end points.

Intervention: Drug interventions with effects on serum PTH, phosphorus, and calcium levels, including vitamin D compounds, phosphate binders, cinacalcet, bisphosphonates, and calcitonin.

Outcomes: Correlation between drug effects on biochemical and all-cause and cardiovascular mortality.

Results: 28 studies (6,999 participants) reported both biochemical and mortality outcomes and were eligible for analysis. Associations between drug effects on surrogate biochemical end points and corresponding effects on mortality were weak and imprecise. All correlation coefficients were less than 0.70, and 95% credible intervals were generally wide and overlapped with zero, consistent with the possibility of no association. The exception was an inverse correlation between drug effects on serum PTH levels and all-cause mortality, which was nominally significant (−0.64; 95% credible interval, −0.85 to −0.15), but the strength of this association was very imprecise. Risk of bias within available trials was generally high, further reducing confidence in the summary correlations. Findings were robust to adjustment for age, baseline serum PTH level, allocation concealment, CKD stage, and drug class.

Limitations: Low power in analyses and combining evidence from many different drug comparisons with incomplete data across studies.

Conclusions: Drug effects on serum PTH, phosphorus, and calcium levels are weakly and imprecisely correlated with all-cause and cardiovascular death in the setting of CKD. Risks of mortality (patient-level outcome) cannot be inferred from treatment-induced changes in biochemical outcomes in people with CKD. Similarly, existing data do not exclude a mortality benefit with treatment. Trials need to address patient-centered outcomes to evaluate drug effectiveness in this setting.

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INDEX WORDS: Renal failure; surrogate endpoint; drug effect; biomarker; parathyroid hormone (PTH); phosphorus; calcium; outcomes; death; all-cause mortality; cardiovascular mortality; chronic kidney disease–mineral and bone disorder (CKD-MBD); phosphate binders; vitamin D compounds; calcimimetic agents; bisphosphonates; calcitonin; meta-analysis; dialysis.

From the [1]Department of Medicine, University of Otago, Christchurch, New Zealand; [2]Sydney School of Public Health, University of Sydney, NSW, Australia; [3]Diaverum Medical Scientific Office and Diaverum Academy, Lund, Sweden; [4]Cumming School of Medicine, University of Calgary, Calgary, Canada; [5]CORE: Centre for Outcomes Research and Clinical Epidemiology, Pescara; [6]Department of Translational Medicine, Division of Nephrology and Transplantation, Amedeo Avogadro University of Eastern Piedmont, Novara; and [7]Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy.

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Address correspondence to Giovanni F.M. Strippoli, MD, PhD, Department of Emergency and Organ Transplantation, University of Bari, Piazza Giulio Cesare, 70124 Bari, Italy. E-mail: gfmstrippoli@gmail.com

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Treatment of chronic kidney disease (CKD) or its complications commonly involves modifying biological end points (such as urine protein excretion or blood pressure) with the ultimate aim of improving patient-relevant outcomes, such as survival or delaying end-stage kidney disease.[1] Biological markers have also been used widely as primary outcomes for the evaluation of drug efficacy and to accelerate regulatory approvals based on the assumption that treatment effects on these end points lead to improved outcomes that are relevant to patients.[2-4] Surrogate end points are frequently used in research and clinical practice because they are more sensitive to drug effects, occur more quickly than patient-level outcomes, and are easier to measure, reducing the complexity and duration of research and treatment. However, for a surrogate end point to be clinically meaningful, treatment effects on surrogate outcomes (such as albuminuria) need to reliably predict effects on true end points of clinical value (such as cardiovascular events). Changes in glomerular filtration rate as an end point in clinical trials in CKD have received specific attention from the US Food and Drug Administration recently.[5]

The bone disease that complicates CKD (known as CKD−mineral and bone disorder [CKD-MBD]) is one large-scale example of this practice in which correcting surrogate end points (abnormal serum parathyroid hormone [PTH], phosphorus, and calcium levels) is standard clinical practice in the belief that this reduces mortality and morbidity.[6] These biochemical end points have also been used for the purpose of regulatory approvals and the publicly funded subsidy of drugs, including phosphate binders and vitamin D compounds.[7,8] The prescribing of vitamin D compounds, phosphate binders, and calcimimetic agents to correct serum phosphorus and PTH levels in CKD is ubiquitous in routine clinical practice and suggested by global guidelines.[6] In 2010, the calcimimetic agent cinacalcet was the single most costly drug prescribed for US dialysis patients based on its ability to lower serum PTH levels.[9] Despite the extensive prescribing of these drugs and associated medication costs, there is uncertainty about their effects on cardiovascular and all-cause mortality.[10,11]

We have previously examined the association between serum PTH, phosphorus, and calcium levels and all-cause mortality in cohort studies and found no robust evidence of a strong and consistent association.[12] However, an evaluation of the link between drug effects on these surrogate biochemical end points and patient-centered outcomes in clinical trials is absent. This study evaluates the assumption that drug effects on widely used surrogate end points (serum PTH, phosphorus, or calcium levels) in men and women with CKD are correlated with drug effects on total and cardiovascular mortality within randomized trials.

METHODS

We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[13]

Data Sources and Searches

We searched existing meta-analyses published in the Cochrane Library for trials reporting interventions for CKD-MBD.[14-18] We supplemented data from existing meta-analyses by searching the Cochrane Central Register of Controlled Trials (CENTRAL) through issue 12, 2014, and MEDLINE (through January week 3, 2015) for study reports using highly sensitive search strategies designed by an information specialist without language restriction. We used the search strategies available in the original Cochrane review publications and supplemented these with a specific strategy for trials targeting specific biochemical values of serum PTH, phosphorus, and calcium (Table S1, available as online supplementary material).

Study Selection

We considered randomized studies in any language comparing any intervention for CKD-MBD or kidney transplantation−related bone disease, including phosphate binders, vitamin D compounds, calcimimetic agents, bisphosphonates, and calcitonin, to evaluate any association between drug effects on biochemical end points (serum PTH, phosphorus, or calcium) and drug effects on mortality outcomes. Inclusion criteria were the availability of reported serum PTH, phosphorus, or calcium levels at the end of follow-up or the proportion of participants achieving a specified biochemical target level in all treatment arms together with reporting of one or more mortality event during follow-up. We excluded data about children and from trials in which follow-up was shorter than 12 weeks.

Data Extraction and Quality Assessment

We defined the biochemical outcomes of interest a priori as either the end-of-treatment serum biochemical value (PTH, phosphorus, or calcium) or the proportion achieving a prespecified target range by end of treatment. The mortality outcomes of interest were all-cause and cardiovascular mortality. Data were extracted by one reviewer (V.S.) and double-checked by a second reviewer (G.d.B.). Any disagreements were resolved by discussion.

To avoid double-counting of participants in studies that evaluated a single drug intervention in 2 or more arms (eg, several doses of a single drug in 3 different study arms), we combined event data for the binary outcomes (mortality and biochemical) for all intervention arms of the same drug into a single analysis or extracted data from the highest dose treatment arm for continuous outcomes (end-of-treatment biochemical values). Risk of bias was adjudicated using standard tools generated by the Cochrane Collaboration, including the domains of sequence generation, allocation concealment, blinding of participants or investigators, blinding of outcome assessment, and completeness of outcome data.[19] We also identified reports of sponsor involvement in authorship and/or data analysis or management.[19]

Data Synthesis and Analysis

For each study, the log ratio of mean biochemical values or the log relative proportion of the study population in each arm achieving a prespecified serum target value at the end of treatment for the intervention and control arms were computed together with the respective standard errors. For all studies, the log relative risk

of all-cause and/or cardiovascular mortality was also calculated and the standard error was derived.

We then generated scatterplots of the effect on mortality (relative risk) on the vertical axis and the effect on biochemical outcome (ratio of means for serum biochemical values at end of treatment) on the horizontal axis. The area of the point estimate was proportional to the sample size and contribution of the study to the overall correlation coefficient. In these plots, point estimates indicating benefits for both outcomes (lower end-of-treatment biochemical value and lower mortality with treatment) were seen in the lower left quadrant. We also generated plots of the effect on mortality on the vertical axis and the effect on achieving the biochemical target (relative risk) on the horizontal axis. In these plots, point estimates indicating benefits for both outcomes (higher likelihood of the biochemical target and lower mortality with treatment) were seen in the lower right-hand quadrant.

The association between treatment effects on surrogate end points and mortality outcomes was then quantified using bivariate random-effects meta-analysis. Because the within-study correlation between treatment effects on biochemical and mortality end points was not available in individual studies, we used the approach proposed by Riley et al[20] that combined the between- and within-study correlations into a single parameter. This correlation was estimated assuming a bivariate normal distribution for the relative risk of mortality and the drug effect on the corresponding biochemical outcome (either the ratio of the mean end-of-treatment serum biochemical level or the relative risk of achieving the prespecified biochemical target range). Although a single regression line showing the correlation between drug effects on biochemical end points and mortality would have aided interpretation of the findings, the 2 components of the correlation (between-study and within-study) were inseparable and therefore plotting such a regression line in the scatterplots was not possible. The model was fitted using a Bayesian approach with uninformative normal—N(0, 1,000)—priors for the means' parameters, uninformative uniform—U(0, 10,000)—priors for the variance components, and an uninformative uniform—U(−1, 1)—prior for the correlation. Four Markov chain Monte Carlo chains of 100,000 iterations each were used to compute the posterior distributions, after 10,000 burn-in iterations. We used Gelman and Rubin[21] diagnostics and inspection of trace plots to check for convergence of Markov chain Monte Carlo chains.

We then explored several covariates (mean age, baseline serum PTH level, allocation concealment, CKD stage, and drug class) as sources of heterogeneity in the estimated correlations. Separate bivariate normal models, including each one of the covariates of interest as a linear effect, were fitted to investigate the impact of the covariate on the estimated correlations. For analysis of covariate effects, we also assumed uninformative normal priors.

A 95% credible interval was calculated for all correlations. The Bayesian 95% credible interval is interpreted as having a 95% probability of including the true correlation between surrogate and clinical end points. For an overview of Bayesian methods, we suggest Bland and Altman.[22] An interval that excluded zero indicated a statistically significant correlation between treatment effects on biochemical and mortality outcomes. All statistical analyses were conducted with R statistical software, version 3.1.1 (R Foundation for Statistical Computing), using the JAGS ("Just Another Gibbs Sampler") package (http://mcmc-jags.sourceforge.net/).

RESULTS

Description of Included Studies

We identified 756 citations from electronic searches and 148 studies in previous systematic reviews (Fig 1). There were 32 studies involving 6,999 participants that met our inclusion criteria (Table S2).[2,23-53] The sources of funding in the included studies are reported in Table S3.

Overall, 30 trials reported all-cause mortality data and 13 reported cardiovascular mortality data. No study prespecified analysis of the association of drug effects on intermediary biochemical end points with subsequent mortality outcomes. The median event rate for mortality was 3.0 (range, 0-26.2) per 100 patients and cardiovascular death was 0.1 (range, 0-5.1) per 100 patients, which were 10- to 20-fold lower than median event rates for achieving biochemical targets (PTH, 40.8 [range, 5.1-90.1]; calcium, 61.8 [range, 12.5-94.8]; and phosphorus, 53.4 [range, 36.6-82.8] per 100 patients). Trials had generally small sample sizes with a median of 40 (range, 6-1,053) patients in each treatment arm. Publication date range was 1981 to 2014.

Seven interventions could be evaluated: phosphate binders (3,154 participants), cinacalcet (1,737 participants), vitamin D compounds (537 participants), bisphosphonates (121 participants), calcitonin (16 participants), placebo (1,007 participants), or standard care (727 participants). Eight studies involved participants with stages 1 to 5 CKD, 21 studies involved participants treated with dialysis, and 3 involved kidney transplant recipients. Average study follow-up was 9.9 ± 8.1 (standard deviation) months. The target serum biochemical end points in the contributing trials are described in Table S4.

Risks of Bias

Most studies did not report procedures for sequence generation or allocation concealment (Figs 2 and S1). Sixteen (50%) were double blind. None reported blinded outcome assessment, and withdrawal of randomly assigned participants from analyses was >10% and/or imbalanced between groups in 18 (56%) studies. Fifteen (47%) reported sponsor involvement in authorship and/or data management.

Effect Sizes for Surrogate Outcomes and Death

In 30 studies (6,580 participants), the range of the point estimates for the relative risk of mortality was 0.11 to 5.21, and in 13 studies (4,223 participants), point estimates for relative risk of cardiovascular death were similarly variable (range, 0.14-3.00). Overall, statistically significant effects were seen in 1 of 30 (3%) studies for all-cause mortality and none of the studies reporting data for cardiovascular death. For drug effects on prespecified serum biochemical targets, point estimate ranges were 1.07 to 10.37 for PTH, 0.31 to 61.49 for calcium, and 0.7 to 1.6 for phosphorus. Statistically significant effects were seen in 9 of 13 (69%) studies for PTH, 3 of 7 studies (43%) for calcium, and

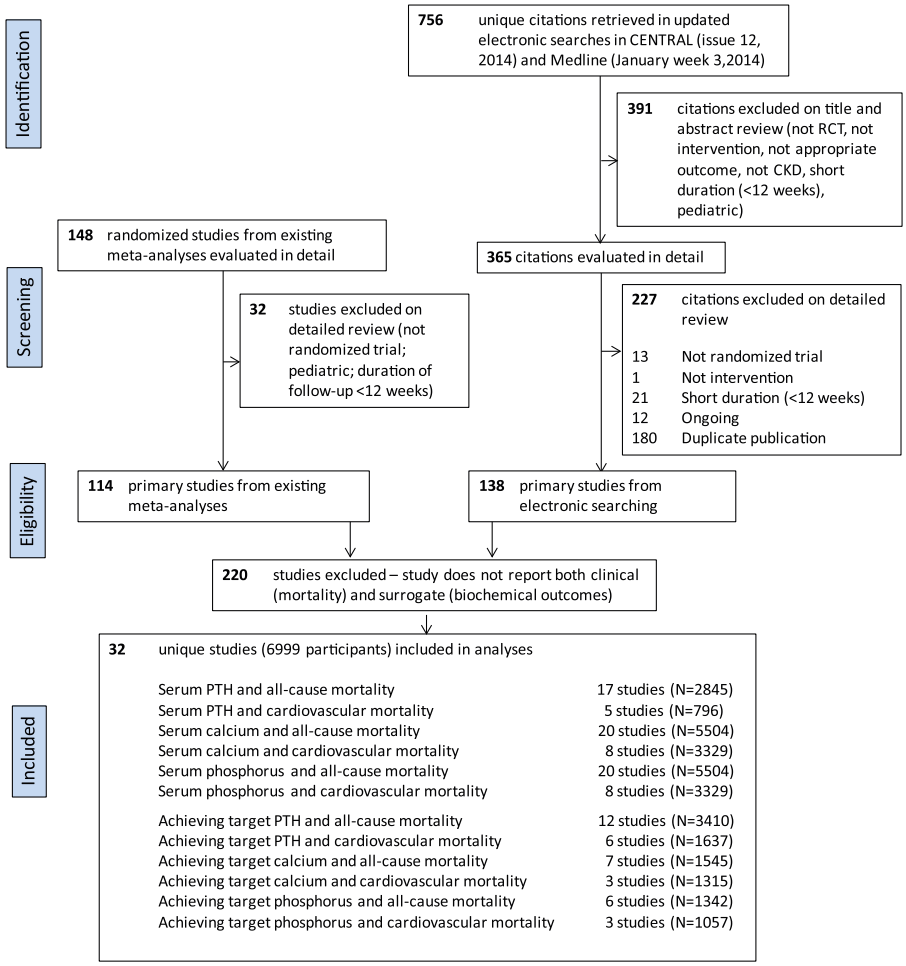

Figure 1. PRISMA flow diagram for identification of included studies.

all but 1 of 7 studies (86%) reporting treatment effects on phosphorus. Point estimates for effects of drugs on serum biochemical values at end of treatment varied from −522 to 207 pg/mL for PTH with statistical significance in 13 of 18 studies (72%), −1.0 to 0.7 mg/dL for calcium with significant effects in 9 of 21 studies (43%), and −1.25 to 0.96 mg/dL for phosphorus with statistical significance in 8 of 22 studies (36%).

Correlations of Effect Sizes

Scatterplots indicated variable and inconsistent associations between treatment effects on achieving target

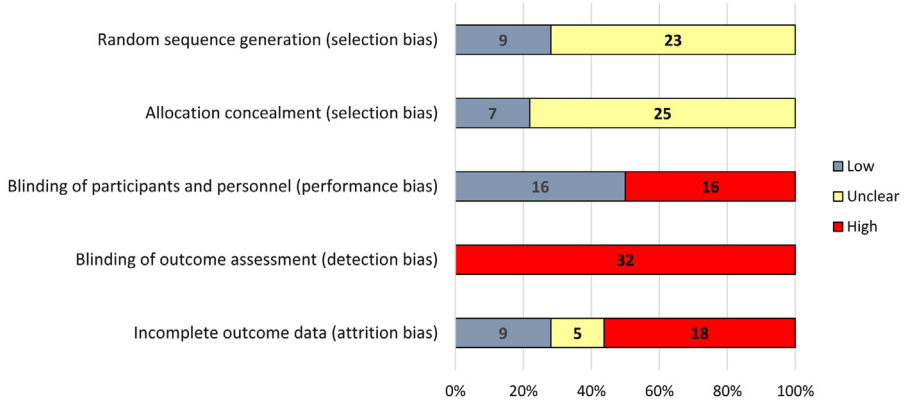

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias domains in included studies. The risks of bias in standard domains are reported according to criteria established by the Cochrane Collaboration. The numbers within the bars show the numbers of trials adjudicated as low, unclear, or high risk of bias for each domain.

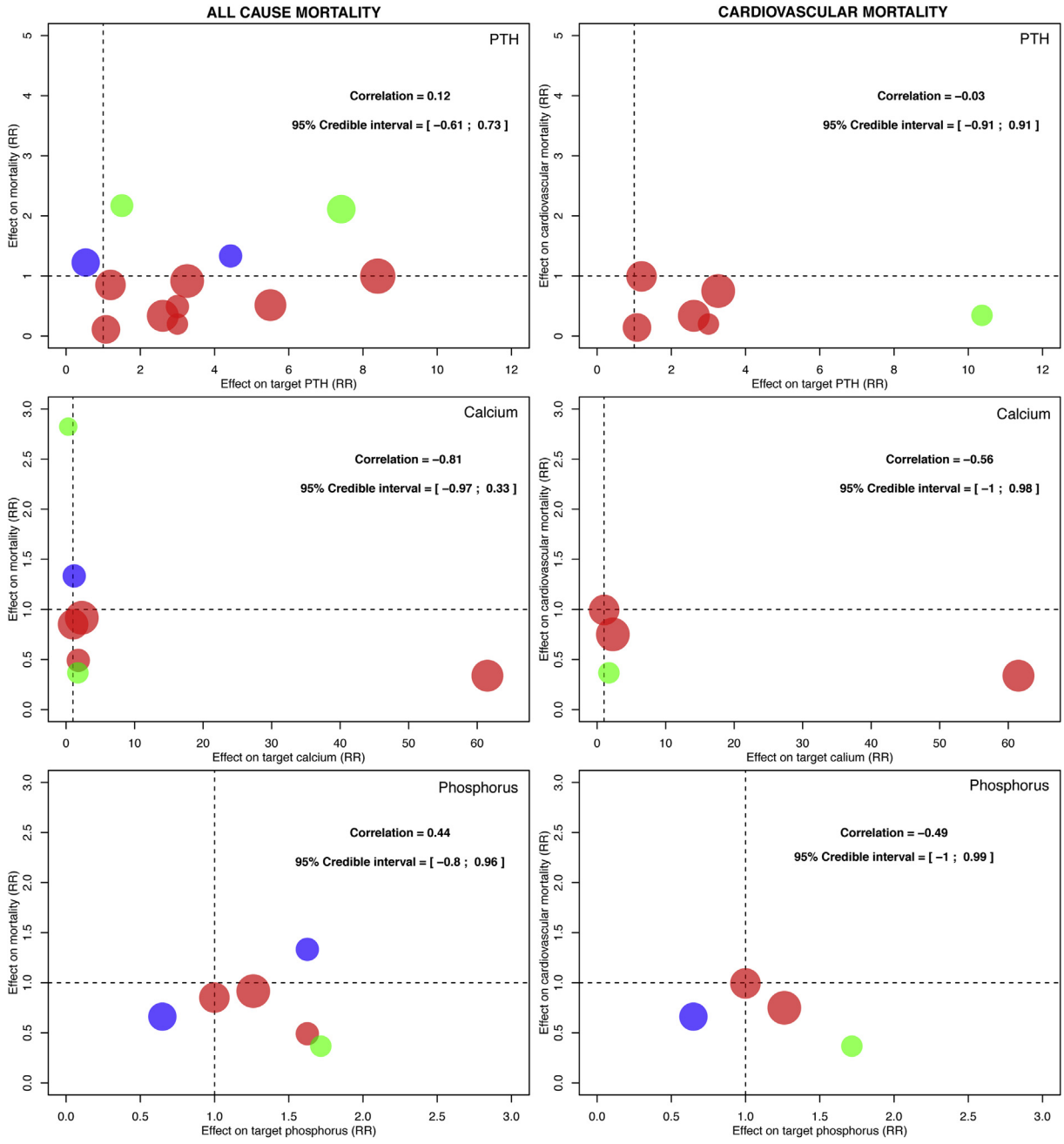

Figure 3. Study-level assessment of the association between relative drug effects on achievement of a target biochemical value (serum parathyroid hormone [PTH], phosphorus, and calcium) and mortality (all-cause and cardiovascular) outcomes. Each point represents the association between the relative drug effect on achieving a prespecified serum biochemical target value (horizontal axis) and the relative risk of all-cause or cardiovascular mortality (vertical axis) within a single study. A point estimate indicating a relative beneficial effect of the active intervention compared to another treatment, placebo, or standard care (lower mortality and achievement of biochemical target range) would be seen in the lower right quadrant. The colors represent different drugs as active treatment (calcimimetic = red; phosphate binder = blue; vitamin D = green). The area of each point is proportional to the sample size of the contributing study. The Bayesian correlation of the effects of drug treatment on biochemical and mortality end points estimated using bivariate metaregression is shown together with the 95% credible interval. A 95% credible interval that includes zero is consistent with no statistical evidence of correlation.

biochemical outcomes and mortality (Fig 3) and mean end-of-treatment biochemical levels and mortality (Fig 4). Bivariate modeling confirmed this visual interpretation, finding weak and nonsignificant correlations between surrogate and clinical end points across the range of outcome combinations. Correlations between effect sizes for biochemical and mortality outcomes were all less than 0.70, and the 95% credible intervals for all

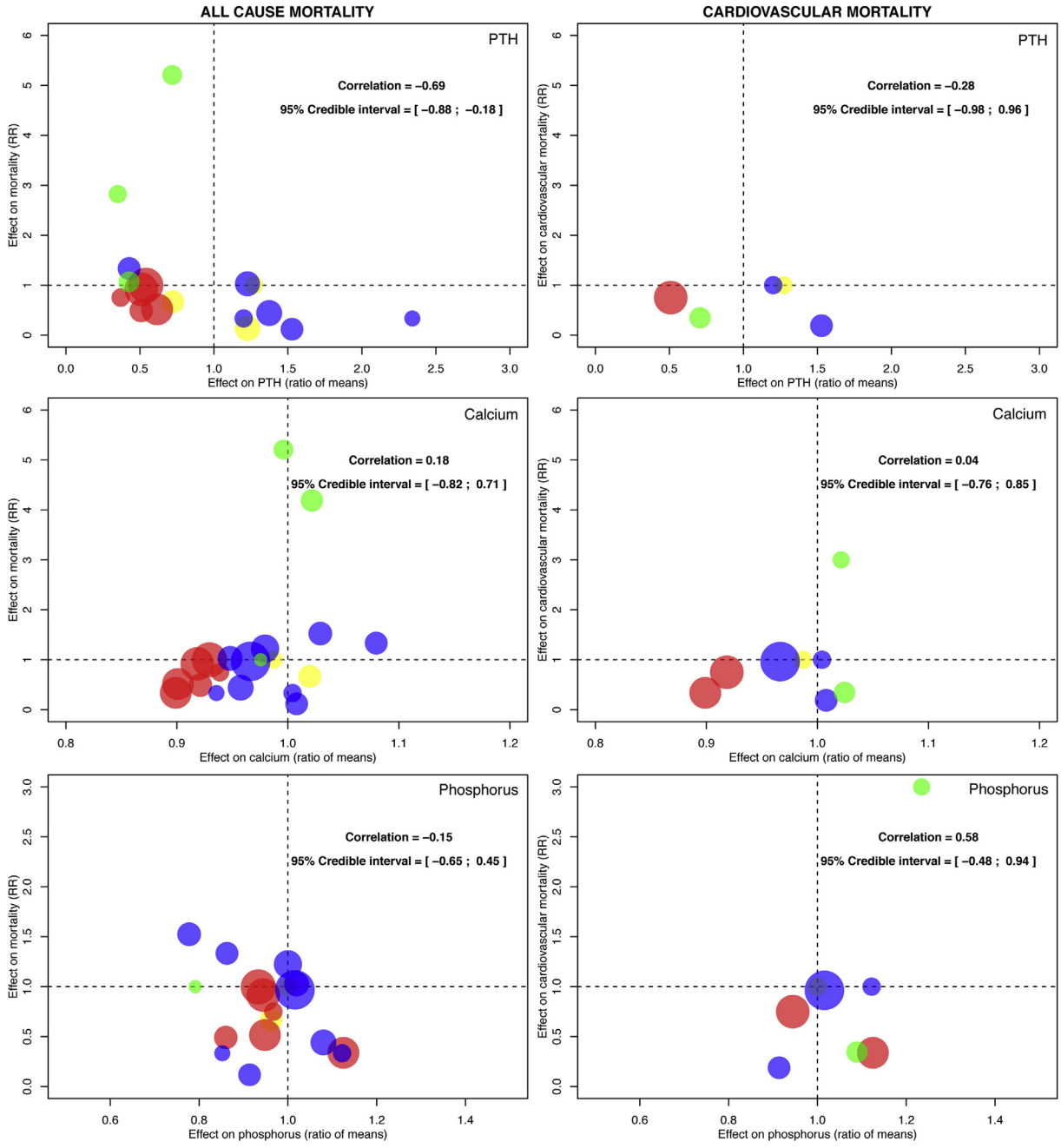

Figure 4. Study-level assessment of the association between relative drug effects on biochemical end points as continuous outcomes (serum parathyroid hormone [PTH], phosphorus, and calcium) and mortality (all-cause and cardiovascular) outcomes. Each point represents the association between the relative drug effects on serum biochemical end points as the ratio of mean end of treatment serum value between the treatment groups (horizontal axis) and the relative risk of all-cause or cardiovascular mortality (vertical axis) within a single study. A point estimate indicating a relative beneficial effect of the active intervention compared to another treatment, placebo, or standard care (lower mortality and lower serum biochemical value with treatment) would be seen in the lower left quadrant. The colors represent different drugs as active treatment (bisphosphonate = yellow; calcimimetic = red; phosphate binder = blue; vitamin D = green). The area of each point is proportional to the sample size of the contributing study. The Bayesian correlation of the effects of drug treatment on biochemical and mortality end points estimated using bivariate meta-regression is shown together with the 95% credible interval. A 95% credible interval that includes zero is consistent with no statistical evidence of correlation.

correlation coefficients overlapped with zero, consistent with evidence of no correlation. The exception was a significant but imprecise inverse correlation between mean drug effects on serum PTH level and all-cause mortality (correlation coefficient, −0.64; 95% credible interval, −0.85 to −0.15), suggesting with considerable uncertainty that a higher serum PTH value following drug treatment correlated with lower total mortality.

Adjustment for Covariates

Findings were similar when we adjusted correlations between biochemical end points and all-cause mortality for key covariates including age, stage of kidney disease, drug used, study methodology, and serum PTH level (Table S5). In adjusted analyses, correlation coefficients remained less than 0.70 (or −0.70) with 95% credible intervals that included the possibility of no correlation. The exception was the inverse association between serum PTH levels and all-cause mortality, which remained statistically significant yet imprecise when analyses were adjusted for baseline serum PTH level, CKD stage, and some drug treatments (bisphosphonate or calcimimetic agent).

We examined correlations between biochemical end points and mortality outcomes separately in studies involving participants treated with dialysis and those with CKD (Figs S2 and S3). Results for participants treated with dialysis were largely similar to the main analyses. Data were considerably sparser for those with earlier stages of CKD and robust conclusions could not be drawn.

DISCUSSION

We found that the effects of a broad range of drugs used widely in CKD to correct perturbed serum PTH, phosphorus, and calcium levels generally do not correlate with cardiovascular and all-cause mortality in randomized trials, although the effects of these drugs in standard clinical practice are universally measured based on improvements in levels of such biomarkers. Although most studies showed large effects on PTH, calcium, and phosphorus levels, drug effects on mortality outcomes were much smaller and generally not statistically significant. Few available studies reported both surrogate and clinical end points sufficiently to be included in analysis. Biochemical end points were at best weakly correlated with mortality and the only statistically significant association observed between serum PTH levels and death was very imprecise. Findings were similar when adjusted for age, severity of kidney disease, study quality, serum PTH level, and drug class. These findings suggest there is little evidence that the effects of drug treatment on biochemical markers for bone disease provide reliable information about cardiovascular mortality or death in people with CKD, which has important implications for trial design, regulatory approval, and clinical practice.

Biochemical end points such as serum calcium and phosphorus levels are plausible end points for drug efficacy in clinical trials because of their putative mechanistic contributions to vascular calcification and injury.[54] However, this study showing weak or no correlations between drug effects on biochemical end points and mortality outcomes together with our previous study showing a generally poor evidentiary basis for associations between these biochemical markers and patient-level outcomes in cohort studies suggests these markers are unsuitable as indicators of drug efficacy.[12] Elsewhere in CKD, well-known examples of frank discordance between proposed beneficial drug effects on a biochemical outcome and mortality (eg, erythropoiesis-stimulating agents increase hemoglobin levels but also increase mortality)[55] suggest caution is needed before accepting biochemical outcomes as relevant to drug research. Validated surrogate markers of treatment effect and safety are few in clinical practice and research.[56]

This meta-analysis highlights the possibility that mortality, although a critical outcome for drug effects and safety in CKD, might not be the optimal patient-relevant outcome in randomized trials in this clinical setting. Despite mortality rates of 10% to 20% per year for patients treated with dialysis, all-cause and cardiovascular deaths were uncommon in studies in this review and drug treatment had no demonstrable effect. This might be because the studies had relatively small sample sizes (median, 40 participants) and because of their brevity (<11 months), which yielded low statistical power. Alternatively, although it is implied that drug effects on biochemical outcomes such as phosphorus and PTH levels modify clinically relevant outcomes in CKD because of their assumed role in the causal pathways of vascular calcification and injury, the pathologic mechanisms causing death in these patients are poorly understood. It is possible that these drugs have no tangible effects on relevant biological pathways leading to health outcomes, although they appear to favorably modify intermediate biochemical markers and vascular calcification.[57] In addition, drugs for bone disease may only partially modify some pathophysiologic pathways causing cardiovascular disease that are mediated through the biochemical outcomes under study, but fail to modify other competing causes of death or morbidity that are equally biologically relevant, and lead to a null overall drug effect. On the basis of these findings, the central role of surrogate biochemical markers of bone disease in the drug management of CKD appears to be of uncertain clinical value.

Treatment of abnormal serum PTH and phosphorus levels in CKD may have other beneficial effects that have not been adequately addressed in existing randomized trials.[10,11,14] The condition CKD-MBD is also associated with hospitalization, itch, fracture, bone pain, muscle weakness, impaired physical function, and health-related quality of life, which are all relevant outcomes for clinical research.[58] Because patients with CKD highly value developing better

drugs to reduce complications from bone disease,[59,60] such "nonmortality" outcomes represent appropriate and potentially high-signal end points for future drug trials that need to be considered in study design and regulatory approvals of new agents.[11,14,15,18]

Several actively recruiting drug trials report PTH levels or other biological measures such as coronary artery calcification as primary outcomes for evaluating efficacy (ClinicalTrials.gov study numbers NCT01020487, NCT01672047, NCT01651000, NCT01382212, NCT01785875, NCT01447368, and NCT01696279), suggesting that biochemical end points remain as key outcomes in clinical trials in CKD, perpetuating the problems of using potentially unproven biochemical end points in drug evaluation. Although many of these trials are small and in the evaluative stage of newer medicines, routine capture of patient-centered outcomes such as hospitalization and quality of life and other symptoms within these trials systematically might, when analyzed cumulatively in the future, enhance our understanding of the place of bone disease treatment in clinical practice beyond biochemical end points.

This study has limitations that need to be considered when interpreting the findings. Despite a systematic search of Cochrane databases, the data on which these analyses are based included few mortality outcomes in trials that were generally of short duration (<11 months), leading to low power in meta-analyses. A beneficial effect of altering biochemical outcomes cannot be excluded. This review evaluated correlations between biomarkers and clinical end points but did not directly address whether early drug-induced changes in serum biochemical values could lower subsequent mortality because data were not available. Formal validation of surrogate end points including PTH, phosphorus, and calcium levels (showing that the treatment's effect on a surrogate end point dependably predicts the effect on the true end point) would require individual patient data from trials that have shown large effect sizes for the outcome relevant to patients under study, and which are not currently available. Finally, the trials in this review had key methodological limitations, particularly due to participant attrition and nonblinding of outcome assessment, that reduced our confidence in the conclusions drawn from contributing data. Trials were generally of insufficient duration to determine whether biochemical outcomes might translate into mortality benefits.

In conclusion, drug effects on serum PTH, phosphorus, and calcium levels are weakly and imprecisely correlated with mortality in CKD at best. Inferring that the benefits of drug effects on biochemical end points translate into improved patient-level health outcomes is not possible based on existing evidence. Future trials of drugs for CKD-MBD need to measure outcomes that are relevant to patients, such as pain, itch, physical function, and muscle weakness, while proxies of all-cause or cardiovascular mortality within such trials need to be properly validated if they are to be relevant to clinical practice and drug evaluation.

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Contributions: research idea and study design: SCP, JCC, PM, GFMS; data acquisition: SCP, VS, GdB; data analysis/interpretation: SCP, AT-P, VS, JCC, PM, MT, GdB, MR, GFMS; statistical analysis: AT-P, PM; supervision or mentorship: JCC, PM, GFMS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. GFMS takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Table S1: Search strategy.

Table S2: Characteristics of included studies.

Table S3: Reported sources of funding in included studies.

Table S4: Target values for serum biochemical end points in included studies.

Table S5: Correlations between all-cause mortality and biochemical outcomes adjusted for specified covariates.

Figure S1: Risk of bias summary: judgments about each risk of bias item for each study.

Figure S2: Subgroup assessment of association between relative drug effects on biochemical end points and mortality outcomes in dialysis.

Figure S3: Subgroup assessment of association between relative drug effects on biochemical end points and mortality outcomes in CKD.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.03.036) is available at www.ajkd.org

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