ASSOCIATION OF SURROGATE ENDPOINTS (SERUM PARATHYROID HORMONE, CALCIUM AND PHOSPHORUS) WITH MORTALITY IN CHRONIC KIDNEY DISEASE TRIALS: A META-ANALYSIS

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Background

In observational studies, elevated levels of serum phosphorus, parathyroid hormone and calcium are associated with vascular calcification, cardiovascular events and mortality. Intervention trials to manage perturbed mineral metabolism in chronic kidney disease commonly use surrogate endpoints to evaluate drug efficacy (serum parathyroid hormone and phosphorus). We evaluate whether treatment-related changes in surrogate endpoints of mineral and bone disorder are associated with risk of mortality in individuals with chronic kidney disease.

Methods

We searched existing meta-analyses and Cochrane databases to February 2014. We included randomized controlled trials of treatment comparisons in chronic kidney disease that reported both biochemical endpoints (serum parathyroid hormone, calcium and phosphorus) together with event data for all-cause or cardiovascular mortality. The association between treatment effects on mortality and treatment effects on the surrogate endpoint was calculated for each individual study. The association between treatment effects on surrogate endpoints and mortality outcomes was quantified using bivariate random effects meta-analysis. The between-study correlation was estimated using a Bayesian approach.

Results

In 28 studies (6473 participants), there were weak and imprecise associations between treatment effects on surrogate endpoints and the corresponding risks of mortality. Correlations between surrogate and mortality endpoints were all ≤0.6. Only one of the 12 estimated correlations was nominally statistically significant, namely: PTH and all-cause mortality, -0.60 [-0.85, -0.16], but the 95% credible interval was very uncertain. Risks of bias in randomization processes, allocation concealment and loss of randomized participants from analyses within studies were high.

Figure 1. Flow chart for identification of included studies

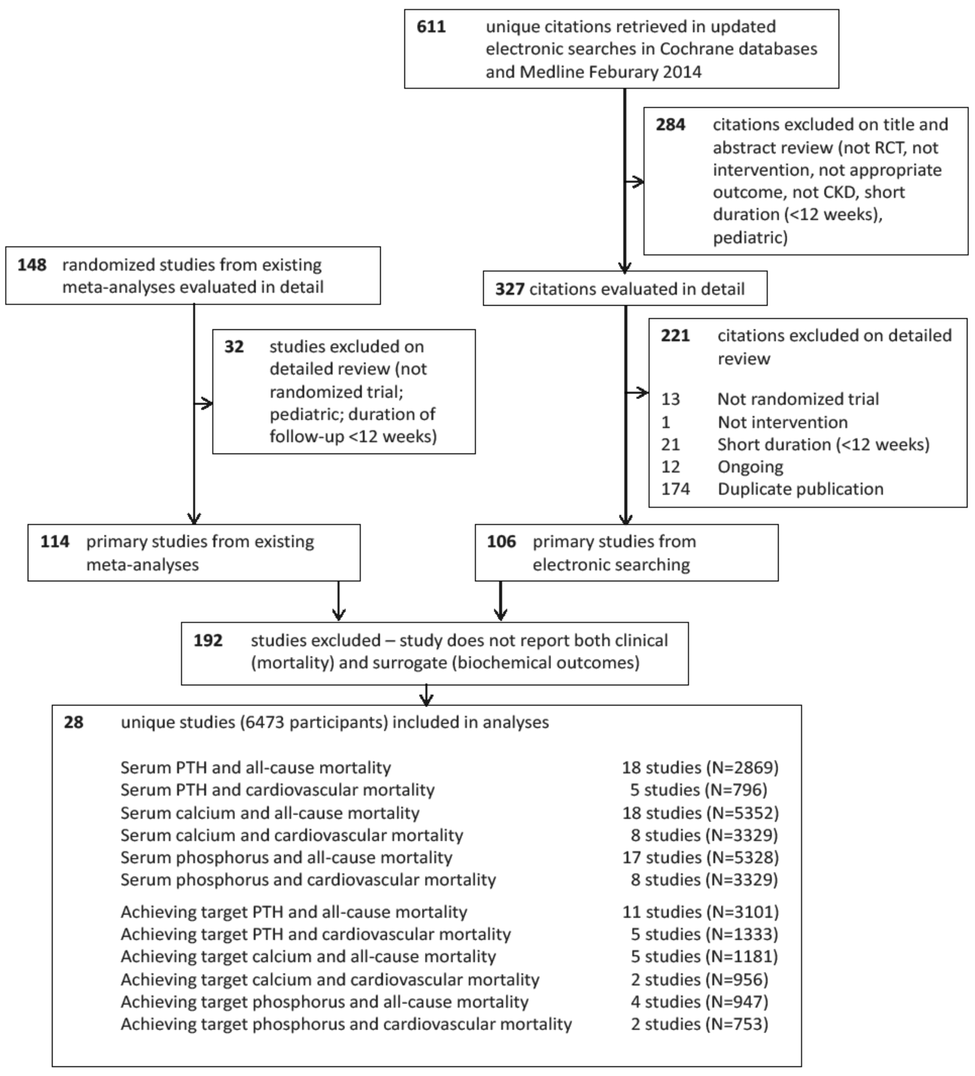
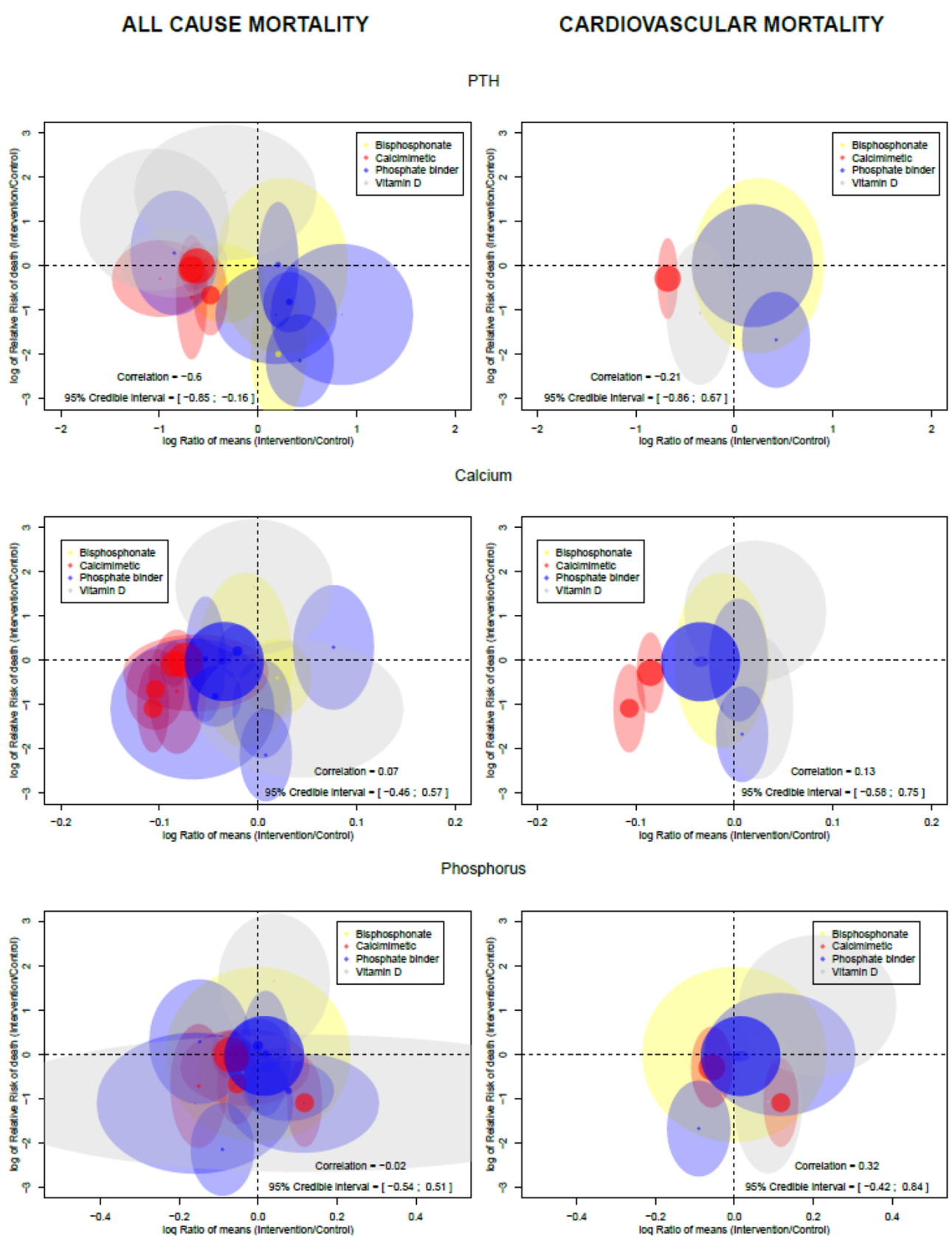


Figure 2. Study-level assessment of the association between treatment-related effects on biochemical endpoints



Conclusion

Levels of serum parathyroid hormone, phosphorus, and calcium are weak surrogate endpoints for all-cause and cardiovascular death in the setting of chronic kidney disease. Treatment effects captured by changes in serum parathyroid hormone, calcium or phosphorus levels are imprecise signals for drug evaluation in nephrology trials.

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