Title
Vitamin D Use and Mortality in Chronic Kidney Disease: Immortal Time Bias—Reply

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Despite the broad use of RAAS-blocking strategies in the United States, the incidence of ESRD and CKD, especially among US patients with diabetes, continues to rise.[2] In March 2007, the US Centers for Disease Control and Prevention reported a 15.9% increased incidence of CKD in the US population 20 years or older during 1999-2004 vs 1988-1994.[2] Such observations and trends have led to increasing concerns of iatrogenic ESRD and CKD associated with RAAS blockade.[3,4] Suissa et al[3] recently demonstrated an increased rate ratio of ESRD of 4.2 in diabetic patients after 3 years or longer of angiotensin-converting enzyme inhibition. More recently, in 2008, we have published reports from several prospective longitudinal cohort studies that demonstrate potentially reversible late-onset renal failure from angiotensin blockade, especially in older patients with CKD, with and without precipitating risk factors.[4] Furthermore, the time-tested argument for a renoprotective benefit of RAAS blockade beyond blood pressure lowering was questioned by a recent subset analysis of the Heart Outcomes Prevention Evaluation (HOPE) study, which demonstrated that the ramipril group achieved substantially greater reductions in arterial blood pressure than the placebo group, as measured by ambulatory blood pressure monitoring.[5]

While we agree with current evidence-based guidelines regarding the utility of RAAS blockade for cardiorenal protection, attention must be drawn to the fact that the large RAAS blockade trials whose findings have led to the increasing application of RAAS blockade in medicine often enrolled younger patients, who often have fairly preserved renal function, usually used lower end doses of these agents, and were often relatively short-term studies.[4] We argue that the benefits of RAAS blockade—improved cardiorenal protection and better patient outcomes—would be better served if the need for a paradigm shift to address these concerns is acknowledged. The treating physician should be ready to consider trial withdrawal of RAAS-blocking therapy in the presence of an otherwise unexplained acute drop in estimated glomerular filtration rate. In addition, in our experience, the temporary withholding of RAAS-blocking therapy before major vascular surgical procedures, during severe illness, and before parenteral contrast administration will only help improve cardiorenal protection and patient outcomes when RAAS-blocking therapy is administered. Larger prospective randomized studies to confirm our findings and conclusions are indeed belated.

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Vitamin D Use and Mortality in Chronic Kidney Disease: Immortal Time Bias

We are concerned that the study by Kovesdy et al,[1] showing a large positive association between mortality and activated vitamin D use in patients with chronic kidney disease, may be severely biased. Patients from a single Department of Veterans Affairs medical center were divided into an exposed group (received oral calcitriol, an activated vitamin D compound) and an unexposed group (no calcitriol). Survival analysis for the exposed group began with the date of the first calcitriol prescription. However, for the unexposed group, analysis began with the date of the first parathyroid hormone (PTH) measurement.

This inconsistency in study entry time introduced a specific lead time bias, sometimes called "immortal time bias."[2] Patients whose first PTH measurement predated their first calcitriol prescription could not have died. Those who died before receiving calcitriol would have been classified as unexposed. Excluding "immortal time," as was done in this study (**Figure**), decreases person-time in the unexposed group, causing the mortality rate for this group to be artificially increased. This results in downward bias in the rate ratio (ie, bias away from 1) with the unexposed group as the referent.

To determine how large the bias would be, we conducted a simulation using the Kovesdy et al[1] approach, along with a time-varying method that appropriately accounted for immortal time. We used the following assumptions: (1) treatment had no effect on outcome, (2) time to death followed an exponential distribution, (3) time to treatment initiation followed a uniform distribution, and (4) the follow-up period was 1000 days or less. We considered 3 different scenarios for mean time to death and mean time to treatment initiation. We ran 500 iterations for each scenario; for each iteration, we randomly drew

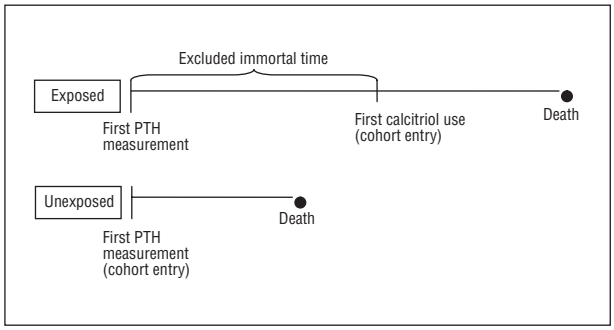

Figure. Timeline of exposed and unexposed subjects. Top panel, misclassified immortal time: vitamin D exposure is defined after a first parathyroid hormone (PTH) measurement, so time between first PTH level and vitamin D exposure, for patients who subsequently receive vitamin D, is immortal. These patients must survive to receive vitamin D and thus are misclassified as exposed during this period, when in fact they are unexposed. Bottom panel, in contrast, cohort entry for unexposed patients is defined by the first PTH measurement.

500 patients and conducted analyses. The relative risks for treatment effect varied from 0.30 to 0.76 (biased) using the Kovesdy et al[1] approach and from 0.98 to 1.01 (unbiased) using our time-varying method. The relative degree of bias detected using the Kovesdy et al[1] approach was mainly dependent on mean time to treatment initiation.

This biased analytical approach likely resulted in overestimation of the event rate in the unexposed group, making calcitriol use appear highly effective compared with no calcitriol use. The authors should redo their analyses, with follow-up beginning at the first PTH measurement for all patients.

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In reply

We thank St Peter et al for their comments about the possibility of immortal time bias in our study that might have affected our reported association between calcitriol therapy and mortality in patients with non–dialysis dependent chronic kidney disease.[1] We agree that this can be a source of bias when examining interventions such as calcitriol therapy, when the group receiving the intervention is entered in the analyses at the time of exposure and the nonexposed group is entered at the time of diagnosis. Indeed, patients who received calcitriol were part of our cohort for a median of 146 days prior to starting the therapy. Several methods have been recommended to address immortal time bias, such as proper matching or time-dependent analyses.[2] We preferred to avoid time-dependent analyses because they would have introduced new sources of bias related to time-dependent confounding and the inconsistency of the methods used for the longitudinal measurements of some core variables such as PTH (as discussed in our article[1]). However, to examine the potential impact of the immortal time of subsequently exposed patients, we conducted several types of sensitivity analyses.

We allocated the time between diagnosis and exposure to the unexposed group using Poisson regressions.[3] The conservatively estimated unadjusted incidence rate ratio associated with calcitriol use in these analyses remained lower compared with noncalcitriol users, although it did not reach statistical significance (incidence rate ratio, 0.78 [95% confidence interval, 0.54-1.12]; P=.17). While this method seemingly addresses the objections of St Peter et al, it also introduces new sources of bias because it results in patients switching exposure groups during the follow-up period and does not allow for appropriate adjustments for important differences between the exposed and unexposed groups.

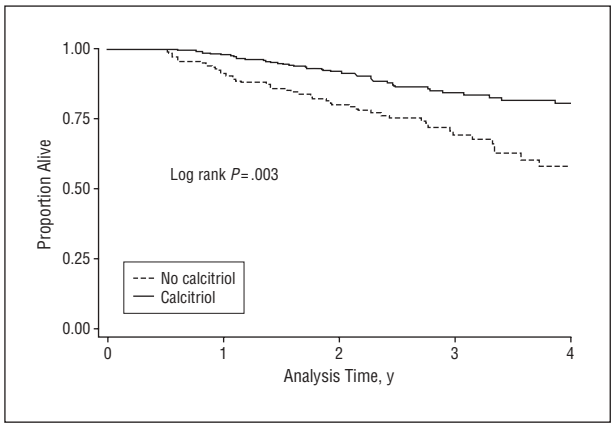

Figure. Kaplan-Meier curves for all-cause mortality, comparing patients treated with calcitriol vs untreated patients, adjusted to age of 70 years, estimated glomerular filtration rate of 30 mL/min/1.73 m^2, and serum parathyroid hormone level of 100 pg/mL (to convert to nanograms per liter, multiply by 1). Untreated patients were only included if they survived for at least 6 months after diagnosis.

*In another sensitivity analysis, we included only unexposed participants with variable length of survival before being entered in analyses to create a more commensurate group for optimal comparison to the calcitriol group. For the 217 patients who did not receive calcitriol (83% of all the unexposed patients in our cohort) who survived at least 6 months (slightly more than the median "immortal time" in the calcitriol group) from the date of diagnosis, the survival curves for the 2 groups showed a gradual and continuous divergence (***Figure***). While the survival advantage of the active vitamin D group was somewhat attenuated compared with our previously reported results, it remained significantly greater than the unexposed group (multivariable-adjusted incidence rate ratio of mortality in the vitamin D group vs the nontreated group, 0.46 [95% confidence interval, 0.29-0.73]; P=.001). Results were similar if using various other lengths of time (up to 1 year) for preanalysis survival in the unexposed group. Results were also similar in additional sensitivity analyses restricting the calcitriol group to patients starting the medication immediately after diagnosis (results not shown).*

It is important to emphasize that the survival advantage associated with calcitriol therapy in our study is in concordance with the results from other large observational studies[4,5] and is based on plausible biological mechanisms.[6] In spite of these observations, we agree that only randomized controlled trials can conclusively determine whether the survival benefit of active vitamin D analogues reported by us and others is causal.

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Limitations of the Anticholinergic Risk Scale

Delirium is common among elderly hospitalized and surgical patients, and a role for anticholinergic agents in precipitating delirium is well recognized.[1] Therefore, we welcome the development of the Anticholinergic Risk Scale (ARS) by Rudolph et al[2] to document anticholinergic activity of various drugs. While the ARS has a substantial subjective component, an objective component is provided by the use of the dissociation constant (pK_i) of various drugs for the cholinergic receptors. However, Rudolph et al[2] do not make clear which cholinergic receptors were used to determine pK_i values of various drugs. Of the 2 known classes of cholinergic receptors (nicotinic and muscarinic), only muscarinic receptors are implicated in anticholinergic effects of drugs.[3] Therefore, the authors have likely used pK_i values of drugs against muscarinic receptors. However, muscarinic receptors are known to have 5 subtypes,[4] and it is important to know which subtypes were used to determine pK_i values. Ideally, the scale should incorporate pK_i values of drugs against each of the 5 subtypes of human muscarinic receptors. Clearly, this is not possible because most drugs have not been tested for their activity against all subtypes of muscarinic receptors. However, the use of pK_i values derived from a mixed population of muscarinic receptors will have limited usefulness, and this should be taken into account.

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In reply

We thank Kwatra for his comments and appreciate the opportunity to respond. The ARS was developed as a tool to identify patients at risk for adverse effects and as an aid to educate clinicians about medications with anticholinergic effects.[1] *In development, the ARS medications were selected and ranked using the following 3 criteria: (1) the pK_i for cholinergic receptors, (2) reports of anticholinergic adverse effects from clinical trials, and (3) relevant MEDLINE searches. There was subjectivity to the selection and ranking of medications on the ARS, and the pK_i was used to provide a degree of objectivity. We focused primarily, but not exclusively, on the pK_i of the human muscarinic-1 (M-1) receptor. Because the pK_i of the human M-1 receptor subtype is not available for all drugs on the ARS, the pK_i of the human general muscarinic, other muscarinic subtype (M-3, M-2, and M-5), and/or histamine-1 subtype receptors were taken into account if necessary (and when available). However, the pK_i values do not provide the complete clinical picture of anticholinergic adverse effects.*

The mixed population of pK_i values does not diminish the clinical utility of the ARS for 3 reasons. First, the relationship between the results of muscarinic receptor binding assays and clinical adverse effects have not been fully established. Next, the use of clinical trial adverse effect reports and medical literature for the ARS medication selection and rank was important for face validity. Finally, the ARS score was validated with patient-reported adverse events that are clinically important outcomes. In the future, we believe that the use of pK_i data within the ARS will enhance the understanding of the relationship between receptor binding and clinical effects.

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Alendronate, Osteoporosis, and Atherosclerosis

A recent article[1] in the *Archives* showed an association between the risk of atrial fibrillation (AF) and alendronate treatment. This relationship may well be confounded by atherosclerosis, which is a background factor for AF but apparently also for osteoporosis. This possibility was duly but shortly mentioned in the accompanying editorial[2] and should be emphasized because these kind of associations easily capture media attention and may lead to unnecessary concern among physicians and patients.

Although the prevalences of both atherosclerosis and osteoporosis increase with age, various and accumulat-