Mineral Metabolites, Angiotensin II Inhibition and Outcomes in Advanced Chronic Kidney Disease


Division of Renal Diseases and Hypertension, University of Colorado Denver, Aurora, Renal Section, Medical Service, Denver Veterans Affairs Medical Center, University of Colorado School of Medicine, and Renal Division, Denver Health Medical Center, Denver, Colo., Division of Nephrology and Hypertension, University of Utah and Renal Section, Medical Service, Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, Utah, and Renal Section, Medical Service, Veterans Affairs NY Harbor Healthcare System and NYU Langone Medical Center, New York, N.Y., USA

Key Words
Dialysis · Mortality · Phosphorus · Renin-angiotensin inhibition

Abstract
Background: Evidence suggests that the renin–angiotensin–aldosterone system (RAAS) interacts with the vitamin D–fibroblast growth factor 23–Klotho axis. We investigated whether circulating mineral metabolism markers modify outcomes in response to RAAS inhibition in subjects with advanced chronic kidney disease (CKD).

Methods: In this retrospective cohort study, we analyzed the association of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) use with all-cause mortality and dialysis initiation among 1,753 subjects (1,099 CKD, estimated glomerular filtration rate 18 ± 6 ml/min/1.73 m² and 654 end-stage renal disease [ESRD]) from the Homocysteine in Kidney and End Stage Renal Disease (HOST) study. A propensity score analysis accounted for indication bias and Cox regression models adjusted for mineral metabolism markers.

Results: Mean follow-up was 3.2 years; 714 (41%) subjects died and 615 (56%) initiated dialysis. In adjusted analyses, all subjects treated with ACEI/ARB had a significantly lower hazard of death (hazards ratio (HR) 0.81, 95% CI 0.70–0.95, p = 0.007). Those with CKD not on dialysis and treated with ACEI/ARB trended toward a lower hazard of dialysis initiation (HR 0.86, 95% CI 0.73–1.01, p = 0.06). The association with mortality did not differ by level of mineral metabolism marker (p for interaction >0.16); however, the relationship with dialysis initiation differed according to the median serum phosphorus level (p for interaction <0.001).

Conclusions: RAAS inhibition was associated with decreased all-cause mortality independent of disordered mineral metabolism among mostly male HOST subjects with advanced CKD and ESRD. However, among those with CKD not requiring dialysis, the renoprotection associated with RAAS inhibition was attenuated by higher serum phosphorus levels. Further studies are needed to confirm this association.
Introduction

The prevalence of chronic kidney disease (CKD) is high, with over 13% of the US population affected by it [1]. Furthermore, more than 600,000 individuals suffer from end-stage renal disease (ESRD) [2]. CKD and ESRD are associated with significant morbidity and mortality [3, 4]. Therefore, better understanding of the mechanisms that cause CKD progression and evaluation of the efficacy of interventions that slow this process are of paramount importance.

Emerging evidence supports the potential role of abnormalities in phosphorus, intact parathyroid hormone (iPTH), vitamin D and fibroblast growth factor 23 (FGF23) as risk factors for poor outcomes in CKD [5]. Elevated levels of serum phosphorus, even within the normal laboratory range, are associated with kidney disease progression [6] and mortality in CKD [7] and ESRD [8]. FGF23, a phosphaturic hormone, rises early in the course of CKD, likely as a compensatory mechanism to maintain phosphorus homeostasis [9]. Epidemiologic studies have shown that progressively elevated circulating FGF23 levels are independently associated with kidney disease progression, initiation of chronic dialysis, cardiovascular disease (CVD) events and all-cause mortality [10, 11].

Pharmacologic inhibition of the renin–angiotensin–aldosterone system (RAAS) through angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) remains the cornerstone of treatment to slow progression of proteinuric and non-proteinuric renal disease [12–14]. RAAS inhibition may also provide protection against mortality in advanced CKD not requiring dialysis [15–18] and ESRD [19–21]. However, other factors may attenuate the efficacy of these agents. In a post hoc analysis of the Ramipril Efficacy in Nephropathy (REIN) trial, a graded attenuation of the efficacy of ramipril in CKD patients with increased serum phosphorus levels was observed, even when phosphorus levels remained within the normal laboratory range [22]. Aside from this post hoc analysis of the REIN trial, the impact of other markers of mineral metabolism abnormalities and mortality among advanced CKD and ESRD patients on ACEI/ARB therapy has not been investigated. Herein, we report the relationship between the use of ACEI/ARB and the risk of all-cause mortality in subjects with advanced CKD and ESRD, as well as the risk of progression to chronic dialysis in those with advanced CKD not requiring dialysis, and whether markers of mineral metabolism affect these associations in the Homocysteine in Kidney and End Stage Renal Disease (HOST) study [23].

Methods

Study Participants

Details of the HOST study have been described previously [23]. Briefly, the study was a multicenter, prospective, randomized, double-blind, placebo-controlled trial examining the effects of high doses of folic acid, pyridoxine hydrochloride (vitamin B6) and cyanocobalamin (vitamin B12) on death and cardiovascular events in subjects with advanced kidney disease and elevated plasma homocysteine levels. The trial enrolled 2,056 subjects from 36 VA medical centers between September 2001 and October 2003. Subjects were included in the study if they were aged ≥21 years with ESRD receiving either hemodialysis or peritoneal dialysis (n = 751), or with an estimated creatinine clearance (calculated by the Cockcroft-Gault formula) of <30 ml/min but not yet on chronic dialysis (n = 1,305) and an elevated plasma homocysteine level of ≥15 μmol/l.

The institutional review board at each participating HOST site approved the study protocol, and all study subjects provided written documentation of informed consent. Procedures were in accordance with the ethical standards of the institutional review boards and the Declaration of Helsinki.

See online supplementary appendix 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000441684) for demographic, biochemical and clinical data collection and measurement.

Outcomes

The individual outcomes for this analysis were the following: (a) time to death from any cause in the whole cohort and (b) time to initiation of chronic dialysis that occurred at least 3 months after randomization in those with advanced CKD not requiring dialysis at randomization. All fatal events were reviewed and classified by the HOST Endpoints Committee using information obtained from hospital discharge summaries, autopsy reports, Medicare End Stage Renal Disease Death Notification forms or death certificates. Deaths were also tracked with the Beneficiary Identification and Records Locator Subsystem, a VA file used to record deaths and dates [24]. The initiation of chronic dialysis was obtained through subject self-report during the follow-up period, verified by clinic and hospital records at the local site and adjudicated by the HOST Endpoints Committee.

Statistical Analysis

Continuous data are described as mean values with their standard deviations, and dichotomous data are described as percentage frequencies. The chi-square test was used for categorical variables and the analysis of variances test was used for continuous variables to evaluate differences in baseline characteristics between subjects with ESRD and advanced CKD and between subjects using and not using an ACEI/ARB.

A propensity score was developed for the likelihood of receiving ACEI/ARB therapy and was calculated by applying a multivariable logistic regression analysis that included the following variables: age, gender, race, hypertension, diabetes mellitus, smoking, serum albumin level, CVD, body mass index, systolic and diastolic blood pressure, kidney function strata (advanced CKD vs. ESRD), serum low-density lipoprotein cholesterol level and high-density lipoprotein cholesterol level. Performance of the propen-
Mineral Metabolites and RAAS Inhibition in CKD

DOI: 10.1159/000441684

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the whole cohort by presence of CKD and ESRD. Ninety-eight percent of the 1,753 subjects were men, and the mean age of the cohort was 66 ± 12 years. Sixty-three percent had advanced CKD with MDRD estimated GFR of 18 ± 6 ml/min/1.73 m² while 37% had ESRD. There was significant comorbidity among the total cohort: 54% had diabetes, 96% had hypertension and 55% had CVD. The advanced CKD group differed significantly from the ESRD group in all baseline characteristics except for systolic blood pressure, presence of hypertension and CVD and use of beta-blockers and aldosterone antagonists. Phosphorus, iPTH and FGF23 levels were significantly higher while...
25(OH)D and 1,25(OH)2D levels were significantly lower in the ESRD group compared to the CKD group (table 1).

Table 2a shows the baseline characteristics of the cohort according to ACEI/ARB use. Among the total cohort, 870 (50%) subjects were using an ACEI or an ARB. Fifty-three percent of those with advanced CKD were using an ACEI or an ARB, while only 47% of those with ESRD used an ACEI or an ARB. Subjects using an ACEI/ARB were significantly younger, had a higher body mass index and lower plasma FGF23 concentration compared...
to subjects not using an ACEI/ARB. The prevalence of diabetes and hypertension was significantly greater among those using an ACEI/ARB. Notably, the mean serum phosphorus level was above the normal laboratory range in both groups but not significantly different between the two (ACEI/ARB vs. none). The 2 groups did not significantly differ in the levels of the other markers of mineral metabolism (albumin-corrected calcium, 25(OH)D, 1,25(OH)2D and iPTH). Table 2b shows the markers of mineral metabolism by ACEI/ARB use and kidney disease status. As expected, subjects with ESRD have higher phosphorus and FGF23 levels and lower 25(OH)D and 1,25(OH)2D levels compared to those with CKD not requiring dialysis.

ACEI/ARB Treatment and All-Cause Mortality

During the study follow-up period of 3.2 years, fewer subjects taking an ACEI/ARB at baseline died from any cause compared to subjects not taking an ACEI/ARB (640 (37%) vs. 789 (45%), p < 0.001). The propensity-adjusted HR for all-cause mortality was significantly lower in the group taking an ACEI/ARB (HR 0.81, 95% CI 0.69–0.94; online suppl. table 1). There was no change in the association of ACEI/ARB use with all-cause mortality when the model was adjusted for markers of mineral metabolism including albumin-corrected calcium, phosphorus, 25(OH)D, 1,25(OH)2D, iPTH and FGF23 (online suppl. table 1). To further explore the relationship between ACEI/ARB use and mineral bone disorder, we tested the interaction between ACEI/ARB use and each marker of mineral metabolism on time to death and found that there were no significant interactions (all p > 0.15). Kidney disease status did not modify the association between ACEI/ARB use and mortality (p = 0.9 for the interaction ACEI/ARB*kidney disease status). These data suggest that ACEI/ARB is protective against all-cause mortality among subjects with advanced CKD and ESRD despite abnormal mineral metabolism including elevated serum phosphorus and plasma FGF23.

ACEI/ARB Treatment and Progression to ESRD

Among subjects with advanced CKD, the incidence of chronic dialysis initiation was lower in the group taking an ACEI/ARB compared to the group not taking an ACEI/ARB. The propensity-adjusted HR for dialysis initiation among those taking an ACEI/ARB was 0.81, 95% CI 0.69–0.95. Sequential addition of albumin-corrected calcium, phosphorus, 25(OH)D and 1,25(OH)2D did not significantly change the risk of dialysis initiation (online suppl. table 2). When FGF23 was added to the model, the magnitude of the association for dialysis initiation was similar to the others but was only of borderline significance (HR 0.86, 95% CI 0.73–1.01, p = 0.06).

There was a significant interaction between ACEI/ARB use and phosphorus level on dialysis initiation (p < 0.001). To further explore this significant interaction, we tested the association between increasing serum phosphorus levels and dialysis initiation in participants treated and not treated with ACEI/ARB. Among those subjects receiving ACEI/ARB, the adjusted HR for dialysis initiation with increasing serum phosphorus levels was lower in magnitude than HR among those subjects not receiving ACEI/ARB (HR 1.21, 95% CI 1.16–1.27 vs. 1.59, 95% CI 1.45–1.74) suggesting an attenuation in the renoprotective effect of ACEI/ARB with increasing serum phosphorus levels. Notably, the interactions of the remaining mineral metabolism markers (albumin-corrected calcium, 25(OH)D, 1,25(OH)2D, iPTH and FGF23) with ACEI/ARB on dialysis initiation were not significant (p > 0.27).

Discussion

In this post hoc analysis of the HOST study that included subjects with advanced CKD not requiring dialysis and ESRD, we found that RAAS inhibition, through the use of ACEI/ARB, was associated with a significantly lower risk of all-cause mortality and that abnormalities of mineral metabolism did not attenuate this protective benefit. In contrast, among subjects with advanced CKD not requiring dialysis, the association of ACEI/ARB use with risk of progression to ESRD was modified by abnormal mineral metabolism, specifically abnormalities of phosphorus metabolism. Indeed, higher levels of phosphorus diminished the protective effect of RAAS inhibition.

Our results support the findings of other retrospective analyses of ACEI/ARB use in CKD and ESRD populations. A post hoc analysis of the HOPE trial showed that 980 subjects with CKD (creatinine 1.4–2.3 mg/dl and dipstick proteinuria ≤1+) had a higher incidence of the primary composite outcome of death, myocardial infarction or stroke and ramipril reduced the incidence of the primary outcome [15]. Similarly, a post hoc analysis of the SAVE trial, showed a risk ratio reduction of 31% on the composite end point of all-cause mortality, cardiovascular mortality, myocardial infarction and congestive heart failure among participants with CKD (baseline creatinine <2.5 mg/dl) [16]. Another retrospective analysis

Mineral Metabolites and RAAS Inhibition in CKD

DOI: 10.1159/000441684

of the Minnesota Heart Survey showed that greater survival was associated with ACEI/ARB use in subjects with advanced CKD (estimated glomerular filtration rate [eGFR] <15 ml/min/1.73 m²) and CVD [17]. To examine the effect of ACEI/ARB use on mortality as a sole end point in non–dialysis-dependent CKD, Molnar et al. [18] reported on a cohort of 141,413 veterans with CKD (eGFR 50 ± 13 ml/min/1.73 m²), of whom 18% were taking ACEI/ARB and 82% were not. Only 22% of this entire cohort had diabetes, and albuminuria was minimal (spot urine microalbumin/creatinine 33 μg/mg). In both the intention-to-treat and the as-treated analyses, ACEI/ARB use was associated with greater survival. However, the RENAAL study, which examined the use of the ARB, losartan, among diabetics with nephropathy showed no benefit related to overall mortality compared to placebo even though a significant reduction in renal disease progression was observed [12]. Contrary to our study, the subjects included in the RENAAL study had better preserved renal function.

Predictably, among subjects with ESRD a mortality benefit related to ACEI/ARB is not uniform across studies. Similar to our results, some retrospective and observational studies undertaken in the ESRD population demonstrate a reduction in the risk of mortality associated with ACEI/ARB therapy [19–21]. An open-label randomized placebo-controlled trial among ESRD patients showed a significantly reduced risk of fatal and non-fatal CVD events and a trend (albeit non-significant) toward reduced risk of all-cause mortality among those treated with ARB compared to those not treated with ARB [25]. In a multi-center, double-blinded, placebo-controlled trial conducted among ESRD patients with left ventricular hypertrophy, there was a trend toward reduction in the composite cardiovascular end point but the study was underpowered due to fewer than expected events [26]. However, other investigators report no mortality advantage related to ACEI/ARB use. A secondary analysis of the HEMO trial showed no association of propensity score matched ACEI/ARB use with all-cause mortality [27]. In fact, there was a greater risk of heart failure admission among ACEI/ARB users compared to those who did not use ACEI/ARB [27]. Likewise, a randomized controlled trial conducted by Iseki et al. [28] showed no benefit of ARB versus other antihypertensive medication on a composite end point including death among ESRD subjects with hypertension. Similarly, a meta-analysis showed no association ACEI/ARB use with fatal and non-fatal cardiovascular events among subjects with ESRD [29].

It is not surprising that among both CKD and ESRD populations, the mortality benefit of ACEI/ARB is not uniformly demonstrated across studies. In these populations, the mortality risk factors that are mitigated by ACEI/ARB use are not the only ones at play. In our study, which is the first to include both advanced CKD not requiring dialysis and ESRD as one group, we not only evaluated the association of ACEI/ARB use and mortality but also analyzed other risk factors that may influence mortality, specifically markers of mineral metabolism. In this cohort, markers of mineral metabolism do not influence the protective effect of ACEI/ARB use on mortality.

Different from the uncertain relationship between RAAS inhibition and mortality in advanced CKD, it is well-accepted that RAAS inhibition mitigates renal disease progression in both non-diabetic and diabetic proteinuric patients [12, 13]. Furthermore, there is growing evidence suggesting that ACEI/ARB use is renoprotective in patients with advanced CKD and in non-proteinuric CKD without a significant increase in adverse events [30–33].

There are several potential mechanisms by which the RAAS is implicated in kidney disease progression and mortality. An emerging concept is its interaction with the vitamin D–FGF23–Klotho axis. Angiotensin II directly decreases renal Klotho [34, 35], a necessary co-factor for high-affinity binding of FGF23 to its receptor FGFR1, thereby affecting FGF23 and 1-α-hydroxylase [36]. One plausible hypothesis is that angiotensin II-induced down-regulation of renal Klotho expression results in FGF23 resistance [36]. FGF23 resistance could then lead to decreased renal excretion of phosphorus and decreased 1-α-hydroxylase expression leading to worsening 1,25(OH)2D deficiency and higher levels of circulating FGF23, ultimately culminating in worsening renal fibrosis, CKD progression and CVD-related morbidity and mortality.

Our analysis is the first to test whether the renoprotective effects of ACEI/ARB are independent of markers of mineral metabolism. These results are clinically important, as most individuals with advanced CKD display progressive vitamin D deficiency and excess levels of circulating phosphorus and FGF23. Comparable to the post hoc analysis of the REIN trial, which reported an attenuation of the beneficial effects of RAAS inhibition on kidney disease progression among subjects with higher levels of serum phosphorus [22], we found that there was a significant interaction between phosphorus levels and ACEI/ARB use on the risk of progression to ESRD among subjects with advanced CKD not requiring dialysis. These
findings suggest that use of ACEI/ARB for renoprotection is attenuated by increasing serum phosphorus.

Strengths of this study include the large number and diversity of participants with very advanced CKD and ESRD, numerous co-variables, a long follow-up period and the development and inclusion of a propensity score to control for indication bias. Despite these and other strengths, our study has some important limitations. As an observational cohort study, causality cannot be concluded. There was no data on proteinuria, which may influence ACEI/ARB use, kidney disease progression and mortality. There was no differentiation between whether an ACEI or an ARB was used, which in the ESRD population is important because of differences in removal by dialysis. There was no available data on iron status, which may interact with markers of mineral metabolism, specifically FGF23. Furthermore, despite adjustments for potential confounders and a propensity score analysis, confounding may still be present. As our study end points were limited to the progression to ESRD and all-cause mortality, we did not analyze the HOST data for any potential adverse events related to RAAS inhibition or the impact of treatment on other CKD-associated comorbidities. Finally, this study included mostly male subjects (98%; a veteran population); therefore, these results may not apply to females with advanced CKD.

Conclusions

In conclusion, RAAS inhibition, through the use of ACEI/ARB therapy, was associated with a decrease in all-cause mortality independent of disordered mineral metabolism among HOST subjects with both advanced CKD and ESRD. However, among HOST subjects with advanced CKD not requiring dialysis, the renoprotection associated with RAAS inhibition was attenuated by higher levels of serum phosphorus.

Disclosure Statement

This study was supported by the HOST executive Committee and the Department of Veterans Affairs Cooperative Studies Program, by the American Heart Association (12POST11920023) and by a VA Career Development Award 2 (1IKCX001030-01A1). There are no conflicts of interest to report.

References
